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Medical devices made of substances for human health: A challenge in terms of efficacy, safety and sustainability

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Medical devices made of substances for human health: A challenge in terms of efficacy, safety and sustainability

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Editorial: Substance-based medical devices for human health: a challenge of efficacy, safety, and sustainability

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KEYWORDS

substance-based medical device, efficacy and safety, European regulation, therapeutic effect, innovation

Editorial on the Research Topic
Medical Devices made of substances for human health: a challenge in terms of efficacy, safety and sustainability

Alessandro Mugelli and Juan Tamargo Treatments without scientific proof of efficacy and safety are offered to and often used by individuals for their medical needs.

Substance-based medical devices (SBMDs) are medical devices composed of substances or by combinations of substances as defined in Annex VIII, Rule 21 of the European Medical Device Regulation (MDR) (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0745). While SBMDs are similar to medicinal products (MPs) in their presentation and pharmaceutical form, they should achieve their therapeutic effect via a "*non-pharmacological, immunological, or metabolic mechanism of action.*"

Independently of the mechanism of action to reach their therapeutic effect, what is of utmost importance is that the therapeutic claim must be demonstrated by well-designed clinical trials and that the benefit/risk ratio reported when SBMDs are marketed should be corroborated by active postmarketing surveillance. Manufacturers must verify the quality and safety of the substances that are in the SBMD according to the EU legislation for patient safety, but this field also represents an opportunity for innovation and research.

The new MDR has been in force since May 2021. As clearly reported in the perspective articles by Giovagnoni, "the MDR's inclusion of different types of product has created a significant opportunity for innovation." In fact, "the Regulation allowed to repurpose the therapeutic properties of natural complex substances, which were unused, or even considered complementary and alternative medicine, within an evidence-based framework and as part of the healthcare sector."

The aim of this Research Topic is to give the clear message that the healthcare system, the scientific research community, and the industry should be prepared to accept the challenges of this profound regulatory change, transforming this change into opportunities for innovation and health improvement.

Interestingly, in the EU, the regulatory changes on clinical research of MPs as well as the more general regulatory framework of medical devices, and in particular of SBMDs, have

FIGURE 1
Total Downloads and Views of the Research Topic, accessed on May 29, 2023.

undergone a major parallel revision, in the interest of the wellbeing of the citizens, of the quality of science, and of improving study feasibility and homogeneity among EU nations (Rasi and Mugelli). This is particularly important because the SBMD market is increasing and currently represents 11% of the total self-medication market in the EU (Bilia et al., 2021).

SBMDs largely fulfill common medical needs in conditions where drugs can be safely and effectively replaced: this is clearly shown by some examples reported in the Research Topic. For example, in the long-term treatment of obese children and adolescents, an SBMD made of natural fiber complexes has been used in combination with a low-glycemic index diet with or without metformin and reduced body mass index and waist circumference, improved insulin sensitivity with reduction of glucose-metabolism abnormalities, increased insulin reserves, and, finally, improved circulating lipid profiles have been noted (Guarino. et al.; Stagi).

Further medical conditions where SBMDs are used with good efficacy and safety are various gastroenterological functional illnesses where pharmacological agents have limitations. Examples are functional esophageal disorders with typical symptoms (mainly heartburn and regurgitation) not associated with structural, inflammatory, or major motility abnormalities and functional dyspepsia characterized by symptoms like post-prandial fullness, early satiation, epigastric pain, and epigastric burning. Furthermore, several chronic gastrointestinal disorders have no underlying anatomic abnormalities identifiable by routine diagnostic examinations and are characterized by predominant symptoms of abdominal pain, bloating, distension, and/or bowel abnormalities (constipation, diarrhea, or mixed constipation and diarrhea), as in the case of irritable bowel syndrome, functional constipation, and functional diarrhea (Longstreth et al., 2006). The rationale for using SBMDs in these rather common conditions and the randomized and controlled clinical trials able to confirm their efficacy and safety are reviewed by Savarino V et al.

Overall, it is apparent that the MDR requires a demonstration of the claim of clinical efficacy and safety of an SBMD, and, consequently, it is also of paramount relevance to develop studies to investigate their non-pharmacological mechanisms of action. An example of an *in vitro* mechanistic study is reported by Bassetto et al. , with the aim of providing scientifically validated procedures that may contribute to the definition of standard methods assessing the biological evaluation of SBMDs.

Finally, Marchesi et al. discuss the difficulties of classifying some products "neatly and unambiguously as belonging to a regulatory class" (MP, SBMD, food supplement, or food for special medical purposes). They use the case of citicoline in glaucoma because several criteria (commercial strategy, ease of market access, price/reimbursement, and mechanism of action) influence the final classification. Glaucoma is a relevant clinical problem; it affects 67 million people worldwide and is the second leading cause of irreversible blindness. Drugs commonly used for glaucoma aim to decrease intraocular pressure and are mostly administered as eye drops. Complementary and alternative medicine is used as adjuncts to traditional drugs (i.e., prostaglandin analogs, beta-blockers, alpha agonists, carbonic anhydrase inhibitors, and rho kinase inhibitors); oral food supplements and SBMDs (usually as eye drops) are widely used. It is estimated that 5%–15% of glaucoma patients take some form of alternative medicine based only on their impression that it can treat their glaucoma (Hetherington, 2013). In their article, the authors consider citicoline as a significant case study because citicoline has been used as a drug, food supplement, food for special medical purposes, and can be sold as an SBMD. They discuss how difficult it could be to discriminate between a pharmacological and a non-pharmacological mode of action because the mode of action may differ according to associated variables, such as the route of administration, dose, and selection of one of many possible targets.

SBMDs may create a significant opportunity to promote innovation in patient management, increasing the spectrum of treatment choices with a favorable benefit/risk ratio. The close

collaboration of pharmacologists, clinicians, and regulators is absolutely necessary to fully exploit this potential for growth. With this Research Topic, we hope to give the reader an overview of this new and unknown field that will likely have a relevant impact on the future of population health. The readers' interest, as shown in Figure 1, appears to support the relevance of this evolving field.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors AM and JT declared that they were editorial board members of Frontiers at the time of submission. This had no impact on the peer review process and the final decision.

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REVIEW
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Efficacy and Safety of a Polysaccharide-Based Natural Substance Complex in the Treatment of Obesity and Other Metabolic Syndrome Components: A Systematic Review

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Introduction: Metabolic syndrome (MetS) is increasingly common in adults as well as in children and adolescents. However, preventing and treating MetS is one of the most pressing challenges for public health services worldwide. At present, the only approved treatments for MetS are dietary changes and physical activity, which are associated with a high rate of non-compliance. On the contrary, no drugs are licensed to treat metabolic syndrome, although a number of drugs are used to treat individual metabolic abnormalities, which increases the risk of adverse events, particularly in children. Policaptil Gel Retard® (PGR), an oral macromolecule complex based on polysaccharides, has been demonstrated to significantly reduce body weight, peak blood glucose (BG) levels, insulin levels, and lipid levels, providing an interesting non-pharmacological therapeutic option for MetS-associated metabolic abnormalities, especially in younger patients.

Aims: To review available studies on the use of PGR in children, adolescents, or adults with obesity or metabolic syndrome.

Methods: A systematic search of electronic databases for PGR and MetS. A total of six studies were identified and included.

Results: Across four randomized clinical studies and one retrospective clinical study including a total of 359 obese children and adolescents with or without MetS and 157 overweight/obese adults with or without MetS and/or T2DM, a single dose of PGR resulted in a reduction in appetite and postprandial triglyceride levels in younger patients and peak postprandial BG levels in adults. Decreased lipid levels were observed in adults following a normocaloric diet who received PGR for 30 days. As a long-term treatment, in combination

with a low-glycemic index diet with or without metformin, PGR resulted in reduced body mass index and waist circumference, improved insulin sensitivity with reduction of glucose-metabolism abnormalities, increased insulin reserve and, finally, an improved circulating lipid profile, regardless of age. No safety issues were reported.

Conclusion: Policaptil Gel Retard® is an effective and safe non-pharmacological approach to improve the treatment of MetS-associated cardiovascular risk factors in children, adolescents, and adults.

Keywords: Policaptil Gel Retard, metabolic syndrome components, obesity, type 2 diabetes mellitus, metabolic syndrome therapy

INTRODUCTION

Metabolic syndrome (MetS) is a clinical condition with a cluster of risk factors for cardiovascular diseases, including abdominal obesity, hypertension, dyslipidemia, and hyperglycemia or diabetes (Expert Panel on Detection E 2001; National Cholesterol Education Program Expert Panel on Detection E 2002). These factors are regarded as a syndrome rather than individual diseases because they share the same pathophysiological mechanism(s) (Mancia et al., 2010; Nsiah et al., 2015; James et al., 2020). The current diagnostic criteria for MetS in children, adolescents, and adults were defined in 2007 and 2009 by the International Diabetes Federation. Obesity (particularly abdominal obesity) is the primary criterion (waist circumference ≥95 cm in adult men or ≥80 cm in adult women), which should be associated with at least two of the additional criteria: triglycerides (TGs) ≥ 150 mg/dl; high-density lipoprotein (HDL) cholesterol ≤ 40 mg/dl in men or ≤ 50 mg/dl in women (or currently on lipid-lowering treatment); systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg (or ongoing anti-hypertensive treatment); or fasting blood glucose (BG) ≥ 100 mg/dl (Alberti et al., 2009). In children and adolescents, due to substantial changes in the body mass index (BMI) during periods of growth, abdominal obesity is defined by a waist circumference exceeding the 89th percentile of patient's age (Zimmet et al., 2007). The Western lifestyle and diet are the root causes of MetS, obesity, and, subsequently, type 2 diabetes mellitus (T2DM), which all increase health care burdens and costs (Nolan et al., 2011; Bhupathiraju and Hu 2016). Obesity and MetS are becoming "epidemic" among younger age groups, not only in high-income settings but also in developing countries (Kelishadi 2007; Collaborators et al., 2017; DeBoer 2019), making the development of effective treatments to prevent cardiovascular disease and liver-related morbidity and mortality of vital importance (Knowler et al., 2002). Dietary and general lifestyle changes often need to be combined with specific drugs to control single factors such as hypercholesterolemia, hyperglycemia, and hypertension associated with MetS (Koskinen et al., 2017; Rask Larsen et al., 2018; Wang et al., 2018; DeBoer 2019). One of the most used drugs is the insulin-sensitizing agent metformin (MTF). The use of MTF is not advised before overt T2DM has been diagnosed and should be avoided in younger patients (Axon et al., 2016; Weihe and Weihrauch-Blüher 2019; Davidson 2020).

Policaptil Gel Retard® (PGR, European patent no. 1679009) is a natural macromolecule complex of functional constituents of medicinal plants that are selected on the basis of emerging behavior (i.e., the behavior acquired by the final complex when its components are pooled together) in order to generate a final system that displays enhanced water binding and swelling capacities while promoting positive health outcomes (lower cholesterol, improved glycemic control, and normal stools) for which reproducible evidence of clinical efficacy has been published and linked to fiber intake, especially fiber with water-holding capacity (McRorie and McKeown 2017; Fornari et al., 2020). The PGR complex is obtained by combining different types of dietary fiber (from polysaccharide-enriched plant extracts) and processed raw materials, including glucomannan (from *Amorphophallus konjac*) (Martino et al., 2005; Fornari et al., 2020), cellulose (from *Opuntia ficus-indica*), chicory root (*Cichorium intybus*) (Pushparaj et al., 2007; Shim et al., 2016), and mucilage (from *Althaea officinalis*, *Linum usitatissimum*, and *Tilia platyphyllos* Scop) (Mani et al., 2011). Under EU Regulation 2017/745 and EU Directive 93/42/EC (as amended), PGR is classified as a medical device and is controlled for efficacy, safety, and production quality by certified third parties. Quality control includes the monitoring of chemical and physical parameters such as average weight, hardness, and weight loss on drying. Metabolomic fingerprinting is performed by near-infrared spectroscopy, and biological parameters are evaluated through water binding capacity and fiber tests. In the gastrointestinal tract, the PGR complex acts as an active, non-pharmacological system, which, *in vitro* and in experimental animal models, has been shown to reduce the availability of dietary components to both the microbiota and the epithelial cells involved in absorption (Greco et al., 2020).

AIM

This systematic review aims to analyze studies on the activity, efficacy, and safety of PGR in children, adolescents, and adults with obesity or MetS, including data obtained from an animal model study supporting its mechanisms of action.

METHODS

We searched for literature studies in the most relevant electronic databases (MEDLINE, SCOPUS, EMBASE, PubMed, Web of

TABLE 1 | Main characteristics of the clinical studies included in the present review.

First author and year of publication	Age (years) mean ± SD or median (range)	Patients setting	Study design	Sample size number (sex)	Subjects in treatment and comparison groups	BMI mean (SD)	Δ BMI kg/m2 or SDS (Tstart vs. Tend)	Major efficacy endpoint	Main Result
Stagi et al. (2015)	11.7 (8.0–13.6)	Obese children (with family history of T2DM/ obesity)	12 months randomized controlled trial	133 pts (69 M and 64 F)	PGR as add-on vs. LGI or ERD diet only. Arm A: 53 pts: PGR + LGI diet. Arm B: 45 pts: LGI diet only. Arm C: 35 pts: ERD diet only	2.33 (0.57) SDS***	Arm A: 0.52 ± 0.17 SDS. Arm B: 0.24 ± 0.01 SDS‡. Arm C: 0.09 ± 0.04 SDS‡‡‡	Changes in anthropometric measures—glucose–insulin metabolism. serum lipid parameters	1. BMI unaffected by ERD. Significant decrease‡ in BMI in PGR vs. LGI-only group. 2. Significant improvement of HbA1c°° and insulinogenic index° in PGR-treated patients only 3. Total cholesterol decrease by 25% in the PGR group; 18% in the LDI only group; 17% in the ERD only group. TGs and LDL cholesterol not affected by any of the treatments
Stagi et al. (2017)	12.6 (8.1–14.3)	Children with obesity and MetS	12 + 12 months. Retrospective study	180 pts (86 M and 94 F)	PGR as add-on vs. MTF + LGI diet vs. LGI diet only. Group A: 71 pts: PGR + MTF + LGI diet. Group B: 58 pts: MTF + LGI diet only. Group C: 51 pts: LGI diet only	2.44 (0.25) SDS***	Arm A: 0.30 ± 0.03 SDS. Arm B: 0.06 ± 0.02 SDS‡‡‡. Arm C: 0.03 ± 0.02 SDS‡‡‡	Changes in anthropometric measures—glucose–insulin metabolism—serum lipid parameters	1. Significant improvement in BMI‡‡‡ and waist‡‡‡ in MTF + PGR vs. MTF-only group. 2. Significant improvement in HOMA-IR‡‡‡, HbA1c‡‡‡, Matsuda index‡‡‡, and insulinogenic‡ and disposition‡‡ indices in MTF + PGR vs. MTF-only group. 3. Significant improvement in total cholesterol‡‡, HDL‡‡‡, and LDL‡‡‡ in MTF + PGR vs. MTF-only group
(Belligoli and Vettor, 2018)*	Not reported	Adults with overweight or mild obesity	30 days randomized double-blind controlled trial	57 pts (not reported)	PGR or placebo as add-on to lifestyle intervention. Group A: 32 pts: PGR-treated. Group B: 25 pts: placebo-treated	Not reported	Not reported	Changes in anthropometric and postprandial lipids at 30 days postprandial BG after a single dose	1. Similar reduction in HDL cholesterol. 2. Significant reduction in fasting LDL cholesterol°°° only in the PGR group

(Continued on following page)

TABLE 1 | (*Continued*) Main characteristics of the clinical studies included in the present review.

First author and year of publication	Age (years) mean ± SD or median (range)	Patients setting	Study design	Sample size number (sex)	Subjects in treatment and comparison groups	BMI mean (SD)	Δ BMI kg/m2 or SDS (Tstart vs. Tend)	Major efficacy endpoint	Main Result
Fornari et al. (2020)	10.1 ± 1.1	Children with obesity	4 h randomized double-blind controlled trial	46 pts (22 M and 24 F)	PGR vs. placebo. Group A: 23 pts: PGR-treated. Group B: 23 pts: placebo treated	26.2 (3.42) kg/m2	Not applicable	Changes in serum lipids, BG, insulin, ghrelin, GLP-1, and appetite	1. Increase in TGs‡ and appetite score‡‡ significantly lower in the PGR group. 2. Similar increase of BG, GLP-1, and insulin
Guarino et al. (2021)	63.5 ± 6.5	Adults with MetS/T2DM	6 months randomized single-blind controlled trial	100 pts (53 M and 47 F)	PGR or MTF as add-on to lifestyle intervention. Group A: 50 pts: PGR-treated. Group B: 50 pts: MTF-treated	35.5 (4.5) kg/m2	- 6.0 ± 0.5 kg/m^2– 6.0 ± 1.0 kg/m^2	Changes in anthropometric measures glucose–insulin metabolism serum lipid parameters	1. Similar significant reduction in anthropometry and glucose–insulin metabolism parameters. 2. A significant higher decrease‡ in all serum lipid values in the PGR group

*The indicated demographic and anthropometric baseline data, as well as clinical and laboratory baseline data, referring to the treatment groups, does not differ from those of the comparison groups. LGI, low-glycemic index; ERD, energy-restricted diet, defined as a 30%-energy-restricted diet compared to individual daily energy requirements; MTF, metformin; BG, blood glucose; GLP-1, glucagon-like peptide 1; TGs, triglycerides; HbA1c, glycosylated hemoglobin. * Published as an abstract; *** values normalized for chronological age by conversion to standard deviation scores (SDSs); between-group comparison:*‡p < 0.05,‡‡p < 0.005,‡‡‡p < 0.001; within-group change: $^{○}$ p < 0.05, $^{○○}$ p < 0.005, $^{○○○}$ p < 0.001, $^{○○○○}$ p < 0.0005.

Science, and CrossRef) by entering Policaptil Gel Retard® (PGR) as the keyword. A total of five clinical studies, of which four studies were *in extenso*, were retrieved and selected for inclusion in this systematic review. Statistical analysis: we reviewed the studies, extracted the results, and summarized them in tables and figures. We also performed a forest plot analysis to highlight the most critical changes in the explored metabolic parameters by using the program RevMan 5.4 for MacOs (Version 5.4, The Cochrane Collaboration, 2020).

RESULTS

Among the clinical studies, one demonstrated the short-term effect (within 4 h) of PGR on blood glucose regulation in obese children, two dealt with the efficacy and safety of PGR in children/adolescents with obesity or MetS, and two (one abstract and one study in *in extenso*) involved overweight or obese adults with MetS or T2DM, as summarized in **Table 1**. All important parameters evaluated in the long-term studies (Stagi et al., 2015; Stagi et al., 2017; Guarino et al., 2021) are summarized in **Figures 1–3**, in which differences in BMI, HOMA-IR, total cholesterol, and TGs before and after PGR administration are reported, and in **Supplementary Figure S1**, in which the differences in LDL cholesterol per single study are reported. **Figure 4** is a forest plot analysis showing a significant estimated mean difference in favor of PGR vs. control treatments when the individual studies are combined and averaged together for the following outcome measures: BMI SDS, HOMA-IR, total cholesterol, HDL, LDL, and TGs.

We focus on the clinical studies, grouping them according to the age of the participants; however, we also provide a comprehensive description of the preclinical study.

Studies in Children and Adolescents

In a longitudinal randomized clinical study, Stagi et al. (2015) evaluated the effects of PGR in 133 obese children and adolescents (with a BMI above the 95th percentile) with a family history of obesity and T2DM. The subjects were randomized into three different groups, each assigned a specific dietary regime: a low-glycemic index (LGI) diet with PGR, an LGI diet only, and a 30% energy-restricted diet (ERD) compared to individual daily energy requirements. Patients were followed up for 1 year. Baseline, 1-year laboratory measurements, and anthropometric data were compared. A significant decrease in BMI (converted to standard deviation scores, SDS, to normalize for chronological age) was achieved both in the LGI + PGR and LGI-only groups, as compared to baseline (BMI SDS LGI + PGR: T0 2.32 ± 0.53 vs. T1 1.80 ± 0.36, $p < 0.0005$; LGI-only: T0 2.23 ± 0.57 vs. T1 1.99 ± 0.56, $p < 0.05$; **Figure 1**). In the LGI + PGR group, glycosylated hemoglobin [HbA1c (percentage): T0 5.63 ± 0.54 vs. T1 5.37 ± 0.35%, $p < 0.005$],

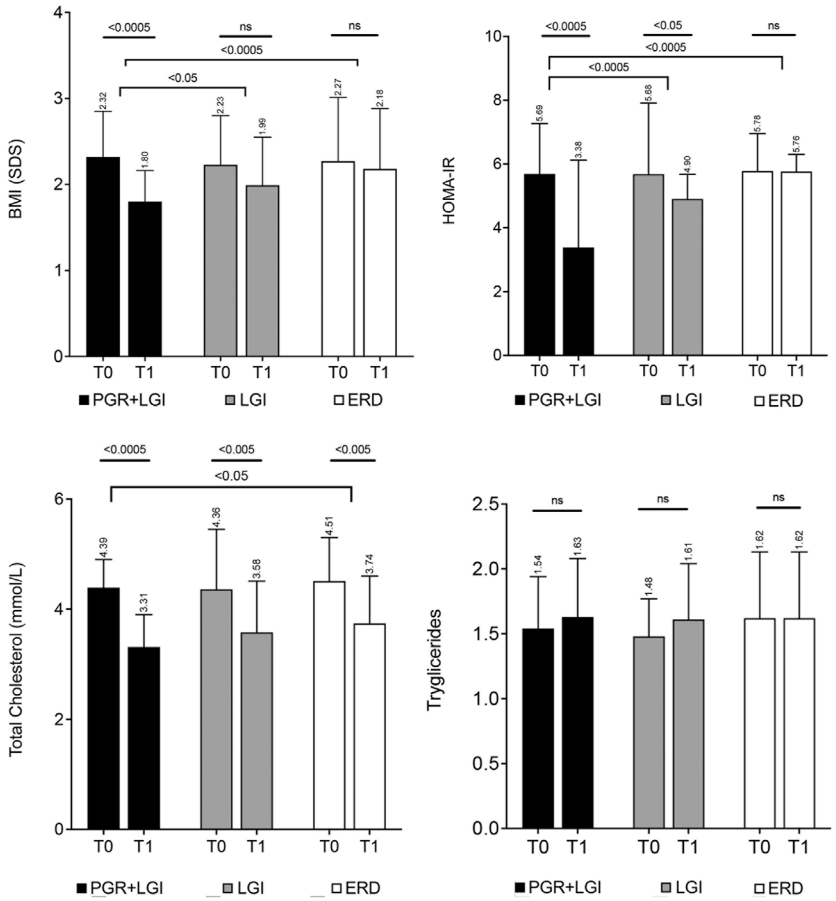

FIGURE 1 | Principal metabolic parameters of the patients involved in the randomized study in children by Stagi et al. (2015). The four panels show the changes in BMI normalized for chronological age by conversion to standard deviation scores (BMI SDS), HOMA-IR, total cholesterol, and triglycerides in the three groups of the study (PGR + LGI: Policaptil Gel Retard plus low-glycemic index diet; LGI: low-glycemic index diet only; ERD: energy restriction diet) from T0 (baseline -first column) to T1 (after 1 year). The PGR-LGI group showed a significant improvement from T0 to T1 in BMI SDS, HOMA-IR, and total cholesterol ($p < 0.0005$) as well as a significantly greater decrease in BMI ($p < 0.05$) and HOMA-IR ($p < 0.0005$) than the LGI group. No significant improvement was obtained in the ERD group, other than that of total cholesterol ($p < 0.05$). The bars represent mean values and standard deviation.

HOMA-IR [mean (range): T0 5.69 (3.60–9.92) vs. T1 3.38 (2.64–5.38), $p < 0.0005$; **Figure 1**], insulinogenic index [mean (range): T0 3.66 (1.90–9.25) vs. T1 2.79 (1.84–8.27), $p < 0.05$], and disposition index [mean (range): T0 4.42 (2.25–11.97) vs. T1 10.28 (5.36–21.65), $p < 0.0005$] significantly improved, compared to baseline, after 1 year, while only HOMA-IR [mean (range): T0 5.68 (2.00–10.90) vs. T1 4.90 (3.15–6.26), $p < 0.05$; **Figure 1**] and disposition index [mean (range): T0 4.01 (0.83–11.72) vs. T1 4.93 (1.53–7.27), $p < 0.05$] significantly improved, compared to baseline, in the LGI-only group. Change in mean absolute values of selected parameters of lipid metabolism (total cholesterol, triglycerides, and LDL cholesterol) together with those of the BMI and HOMA-index, error bars, and within- and between-group differences are reported in **Figure 1** and **Supplementary Figure S1**. Total cholesterol levels improved in all groups with a more significant reduction in the LGI + PGR group (T0 4.39 ± 0.51 vs. T1 3.31 ± 0.59 mmol/L, $p < 0.0005$) than those in the ERD group (T0 4.51 ± 0.79 vs. T1 3.74 ± 0.86 mmol/L, $p < 0.05$), whereas TGs and LDL cholesterol were not affected by any of the treatments (p: ns in all groups, see also **Supplementary Figure S1**).

The addition of PGR to the LGI diet significantly reduced the occurrence of *acanthosis nigricans*, a hyperpigmentation of the skin that is often localized in body folds and on the forehead, which has been linked to insulin resistance and hyperinsulinemia (Sinha and Schwartz 2007). In fact, *acanthosis nigricans*, which was present at baseline in 13.2% (7/53) of subjects in the PGR + LGI diet group, was to be present in 5.6% (3/53) ($p < 0.005$) after treatment. This did not occur in the LGI and ERD diet groups where *acanthosis nigricans* was present in 13.3 and 11.4% of the subjects, respectively, before and after the dietary intervention.

The long-term effects of PGR were also investigated in a retrospective single center study analyzing three cohorts of patients to evaluate PGR added to MTF, both as an add-on to lifestyle intervention (Stagi et al., 2017). Data from 129 obese children and adolescents with MetS treated for a minimum of 2 years with MTF, who were followed at the pediatric hospital, were collected. As per clinical practice, in all patients, MTF

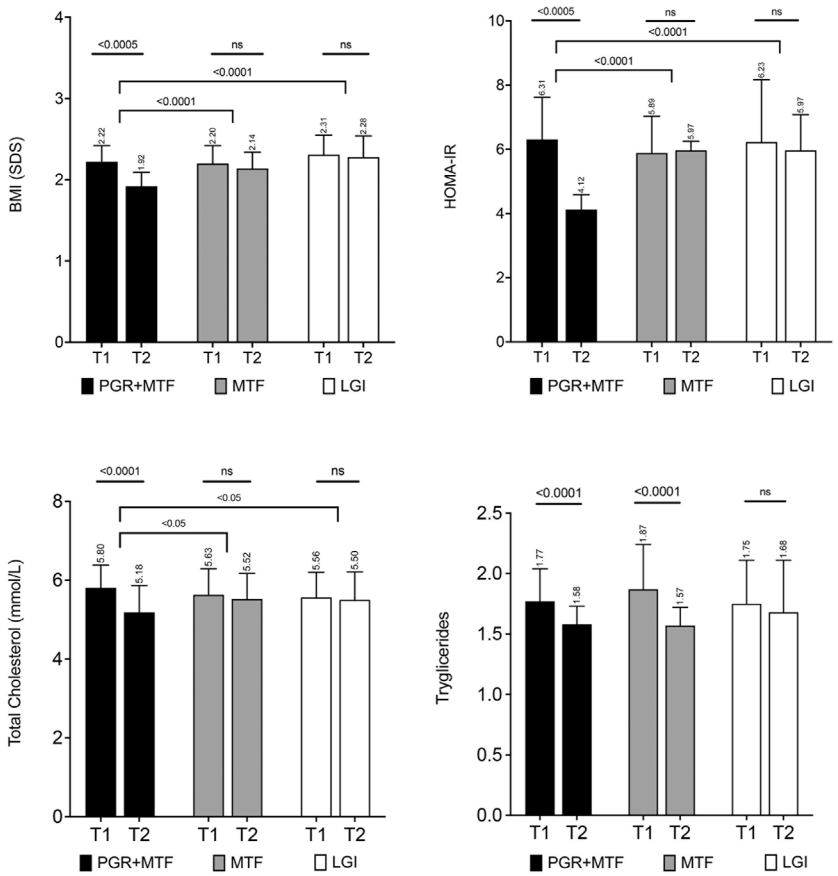

FIGURE 2 | Principal metabolic parameters of the patients involved in the retrospective study in children conducted by Stagi et al. (2017). The four panels show the changes in BMI (SDS), HOMA-IR, total cholesterol, and triglycerides in the three groups whose data were collected (PGR + MTF: Policaptil Gel Retard plus metformin; MTF: metformin alone; LGI: low-glycemic index diet) from T1 (after 12 months of therapy) to T2 (after a further 12 months in which PGR was taken in addition to MTF by patients of the first group). Only the PGR + MTF group showed a significant improvement in BMI (SDS), HOMA-IR ($p < 0.0005$ for each), total cholesterol, and LDL cholesterol (see **Supplementary Figure S1**) ($p < 0.0001$ for each) together with that of triglycerides ($p < 0.0001$) in common with the MTF group. The bars represent mean values and standard deviation.

dosage was progressively increased according to a pre-specified algorithm until reaching the maximum daily dose of 1,500 mg after 4 weeks. After 12 months of MTF, 71 patients voluntarily started PGR as an add-on treatment, whereas 58 patients continued on MTF alone. Both groups followed an LGI diet. The two groups were compared to an historical control cohort consisting of 51 age-, sex-, and BMI-matched subjects with obesity and MetS on an LGI diet only. The same selection criteria were applied for patient inclusion in all groups, which did not differ significantly in auxological and metabolic terms at baseline. Compared to the controls, over the first 12 months, MTF-treated patients displayed a significant reduction in BMI SDS (2.18 ± 0.21 vs. 2.31 ± 0.24, MTF and controls, respectively; $p < 0.005$) and waist SDS (2.78 ± 0.52 vs. 2.99 ± 0.61, MTF and controls, respectively; $p < 0.05$), as well as a significant increase on the Matsuda index (IS_{OGTT} SDS: 1.51 ± 0.22 vs. 1.42 ± 0.24; MTF and controls; $p < 0.05$), i.e., the index of insulin sensitivity calculated from the oral glucose tolerance test (OGTT) (Matsuda and DeFronzo 1999). After the following 12 months, the combined MTF + PGR treatment significantly improved (MTF + PGR group vs. MTF-only group, respectively) BMI SDS (1.92 ± 0.17 vs. 2.14 ± 0.20, $p < 0.001$), waist SDS (2.42 ± 0.43 vs. 2.75 ± 0.43, $p < 0.001$), HOMA-IR (4.12 ± 0.47 vs. 5.97 ± 1.11, $p < 0.001$), HbA1c (5.71 ± 0.28 vs. 5.94 ± 0.26%, $p < 0.001$), total cholesterol (5.18 ± 0.68 vs. 5.52 ± 0.65 mmol/L, $p < 0.005$), HDL cholesterol (1.06 ± 0.11 vs. 0.92 ± 0.15 mmol/L, $p < 0.001$), LDL cholesterol (3.25 ± 0.90 vs. 3.86 ± 0.68 mmol/L, $p < 0.001$), the Matsuda index (IS_{OGTT} SDS: 2.27 ± 0.52 vs. 1.65 ± 0.21, SDS, $p < 0.001$), insulinogenic index (2.24 ± 1.12 vs. 2.97 ± 1.98, $p < 0.05$), and disposition index (6.78 ± 2.99 vs. 4.92 ± 2.56, $p < 0.005$). Absolute values and both within- and between-group differences in BMI, HOMA-IR, total cholesterol, and TGs from the 12th (T1) to the 24th (T2) month are also shown in **Figure 2**. Since no significant differences between MTF and control groups were observed from the 12th to the 24th month across numerous analytical metabolic parameters, i.e., the HOMA-IR (**Figure 2**), Matsuda, insulinogenic, and disposition indices, as well as total (**Figure 2**) and LDL cholesterol (**Supplementary Figure S2**) (p: ns for each). The addition of PGR significantly extended and potentiated the positive effects of MTF treatment, allowing for

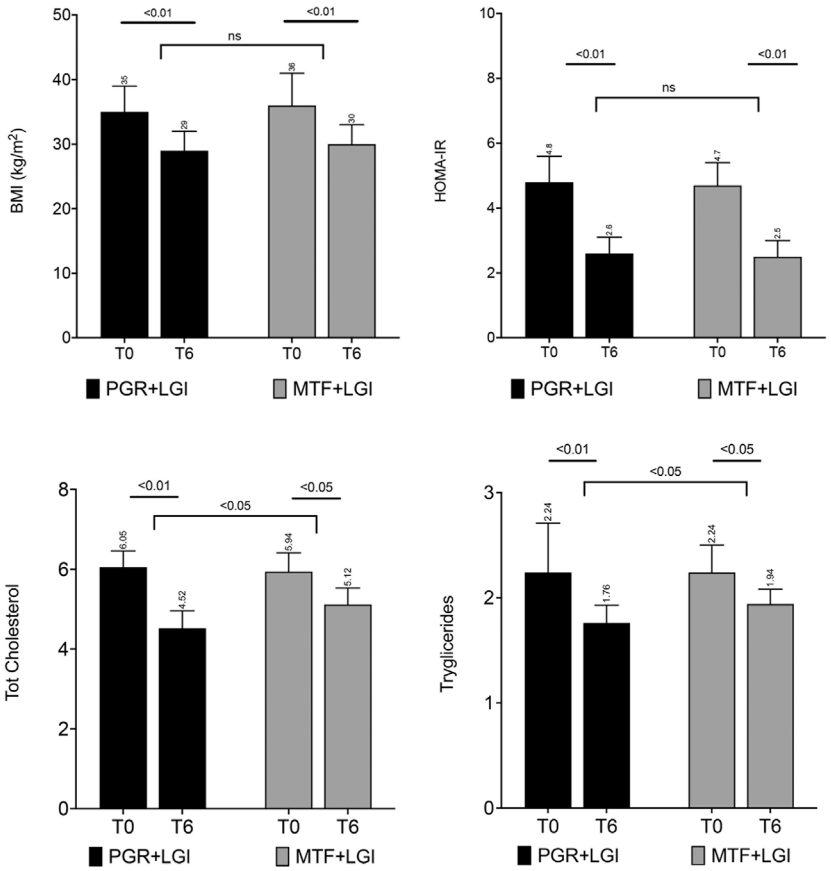

FIGURE 3 | Principal metabolic parameters of the patients involved in the randomized study in adults by Guarino et al. (2021). The four panels show the changes in BMI (SDS), HOMA-IR, total cholesterol, and triglycerides in the two study groups (PGR + LGI: Policaptil Gel Retard plus low-glycemic index diet; MTF + LGI: metformin plus low-glycemic index diet) after 6 months of treatment (T6). Both groups showed significant improvements after treatment in BMI, HOMA-IR ($p < 0.01$ for each), total cholesterol, LDL cholesterol (see **Supplementary Figure S1**), and triglycerides, but a significant between-group difference ($p < 0.05$) in favor of PGR for all serum lipid parameters was also found. The bars represent mean values and standard deviation.

significant further improvement of the adiposity parameters associated with a significant reduction in glucose, insulin, and lipid alterations. Of note, the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) mean values, that were mildly elevated in all groups both at baseline (Patients T0: ALT: 57.23 ± 20.89 U/L; AST: 59.66 ± 27.53 U/L; Controls T0: ALT: 53.67 ± 18.91 U/L; AST: 55.21 ± 24.90 U/L) and after 12 months (Patients T1: ALT: 52.32 ± 20.24 U/L; AST: 53.76 ± 23.19 U/L; Controls T1: ALT: 51.45 ± 17.76 U/L; AST: 53.45 ± 22.84 U/L), showed a significant decrease, as compared to baseline, only in the MTF + PGR group (PGR T2: ALT: 40.02 ± 13.27 U/L; AST: 42.00 ± 17.10 U/L, $p < 0.0001$ vs. T1; MTF T2 ALT: 48.26 ± 14.98 U/L; AST 48.55 ± 16.53 U/L, p:ns vs. T1; Controls T2: ALT 55.67 ± 24.39 U/L; AST: 55.67 ± 24.39 U/L, p: ns vs. T1), with AST significantly decreasing, after PGR treatment, compared to controls ($p < 0.005$) and ALT compared to both the MTF and control groups ($p < 0.05$ vs. MFT and $p < 0.0001$ vs. controls). In these latter groups, mean values remained substantially unchanged.

This study also reports safety and adherence data. During the first 12 months of MTF only, adverse events (AE) were reported in 20.1% of cases (hypoglycemia 2.3%, diarrhea 6.2%, constipation 2.3%, flatulence 4.6%, and abdominal pain 7.0%). These symptoms were reduced or eliminated after a reduction of the dose of MTF with no need to interrupt MTF treatment. Following the addition of PGR between 12 and 24 months, AEs occurred in 16.9% of patients (hypoglycemia 2.8%, diarrhea 5.6%, flatulence 2.8%, and abdominal pain 5.6%), which was comparable to the rate reported before in the MTF-only group. Comparable rates of AEs were also observed in the MTF-only group between 12 and 24 months, except for abdominal pain, which had a frequency of 8.6%. No serious AEs were reported. The adherence to PGR therapy was 91%.

A short-term randomized, double-blind, placebo-controlled trial investigated postprandial changes in the metabolic state and appetite of 46 obese children (Fornari et al., 2020). At baseline and at selected intervals over the course of 4 hours following a mixed meal (15 kcal/kg of lean body mass) consumed 20 min after PGR or placebo, the following parameters were measured: lipid levels (TGs and non-esterified fatty acids (NEFA)), BG, insulin levels, ghrelin, glucagon-like peptide 1 (GLP-1), and

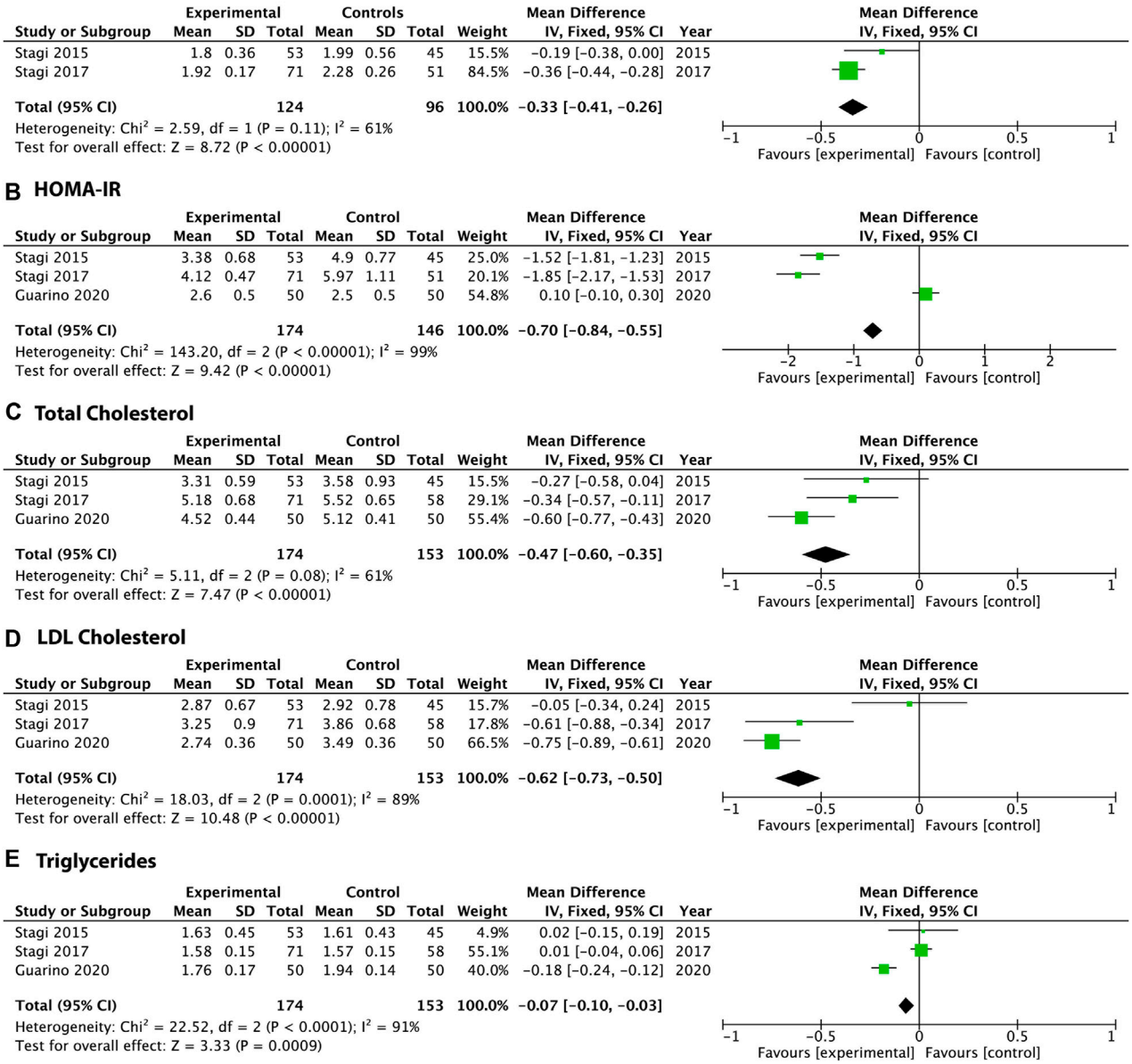

FIGURE 4 | Forest plots of the principal metabolic parameters at the end of the treatment period in three clinical studies, published *in extenso*, that evaluated the administration of PGR to patients with metabolic dysfunction. Even if there were different study designs, different populations (children or adults either fulfilling or not fulfilling the current MetS diagnosis criteria), and different durations, the patients in the experimental groups treated with PGR demonstrated greater improvements in BMI, insulin sensitivity (reduction of HOMA-IR), total cholesterol, LDL cholesterol, and, less markedly, in triglycerides. The meta-analysis was performed with Review Manager software for Macintosh ((RevMan). To evaluate the homogeneity of the studies, we performed a homogeneity test based on the $\chi 2$ calculation. To overcome the low power of the test, a minimum cutoff *p*-value of 0.1 was established as a threshold for heterogeneity. We obtained the pooled estimates, with a relative confidence interval of 95%, through the use of random-effects models. The fourth human study (Belligoli and Vettor 2018) was excluded because of a lack of sufficient data to perform the calculations.

appetite level, measured through visual analog scales (VAS), simplified for children (Flint et al., 2000). The scale was made up of color boxes to improve the children's comprehension of subjective hunger. The incremental area under the curve (iAUCs) for each metabolite and hormone were compared. The increase after 240 min in TGs was significantly lower in the PGR group (+3,021 ± 2,879 mg/dl) as compared to placebo (+5,038 ± 3,738 mg/dl) (p:0.046). NEFA decreased similarly in both groups (p:ns). The iAUC of ghrelin was significantly lower after taking PGR (−8,179 ± 8,073 pg/ml) than after placebo (−2,800 ± 7,579 pg/ml) (p:0.026). Glucose, GLP-1, and insulin increased similarly for both PGR and placebo (p:ns for each), while the appetite score was significantly lower in the PGR group (−234 ± 274 vs. 36 ± 239; p:0.004).

Therefore, the data in children and adolescents demonstrate a positive short-term (i.e., immediately following the administration) effect of PGR on lipid metabolism and appetite in obese children compared to placebo.

Data from the aforementioned studies (Stagi et al., 2015; Stagi et al., 2017) also seem to show that, in the long term, PGR in combination with an LGI diet in obese children and adolescents at high risk of developing MetS (i.e., with a family history of obesity and T2DM) induces significantly greater weight loss and a significant increase in insulin sensitivity than diet alone. In obese children and adolescents with established MetS, PGR enhanced the positive effects of MTF on the adiposity parameters and significantly improved glucose and insulin parameters and lipid profiles compared to patients who were either on an MFT plus LGI diet, or an LGI diet alone.

Studies in Adults

The first study in adult subjects was retrieved as an abstract (Belligoli and Vettor 2018) reporting preliminary data from a randomized, double-blind, placebo-controlled clinical trial involving 63 normoglycemic overweight or mildly obese subjects following a balanced normocaloric diet and a regular program of physical activity, who were treated with PGR or placebo for 30 days. In addition to changes in the anthropometric and postprandial lipid profile data after 30 days, the variation in postprandial BG was studied after a single dose of PGR or placebo. In the single-dose assessment, PGR-treated patients exhibited a statistically significant improvement in their postprandial BG profiles without any differences in the fasting parameters (PGR BG at t30-BG at t60 0.45 ± 0.65 vs. Placebo 0.67 ± 0.76 mmol/L, $p < 0.05$). Due to its publication format as an abstract, several details on the evaluated parameters are lacking. However, the authors stated that after 30 days of intake, PGR was able to significantly reduce LDL cholesterol 300 after a standard meal in comparison with placebo ($p < 0.05$). Moreover, in PGR-treated patients, fasting and postprandial LDL cholesterol and total cholesterol levels were reduced compared to baseline (data not reported by authors; reported statistical significance as < 0.001).

Finally, the authors also report that both groups showed a significant reduction in body weight as well as waist and hip circumference compared to baseline at this early time point without providing further information (data and p values were not available).

In a recent single-blind, randomized trial, 100 adult patients with MetS and T2DM were randomized to either the PGR or MTF group for 6 months as an add-on therapy to background lifestyle intervention (i.e., an LGI hypocaloric diet) (Guarino et al., 2021). MTF was administered at a daily dose of 1,500–2000 mg. Serum lipids, anthropometric measures, glucose–insulin metabolism changes, and safety/tolerability were evaluated at baseline and at 6 months. A similar significant reduction was observed in both groups in BMI (PGR: T0 35 ± 4 vs. T6 29 ± 3 kg/m^2; MTF: T0 36 ± 5 vs. T6 30 ± 3 kg/m^2; $p < 0.01$ for each), waist circumference (PGR: T0 114 ± 10 vs. T6 86 ± 5 cm; MTF T0 115 ± 9 vs. T6 88 ± 5 cm; $p < 0.01$ for each), visceral fat percentage (PGR: T0 23 ± 6 vs. T6 15 ± 4%; MTF T0 24 ± 6 vs. T6 14 ± 4%; $p < 0.01$ for each), HbA1c (PGR: T0 60 ± 15 vs. T6 50 ± 14 mmol/mol; MTF: T0 58 ± 14 vs. T6 50 ± 16 mmol/mol; $p < 0.05$ for each), C-peptide (PGR: T0 1.6 ± 0.5 vs. T6 1.0 ± 1.5 μg/L; MTF T0 1.6 ± 0.5 vs. T6 1.0 ± 1.5 μg/L; $p < 0.05$ for each), fasting plasma glucose (PGR: T0 197 ± 9.0 vs. T6 117.5 ± 10.3 mg/dl; MTF: T0 2.18 ± 0.21 vs. T6 2.31 ± 0.24 mg/dl; $p < 0.01$ for each), and HOMA-IR (PGR: T0 4.8 ± 0.8 vs. T6 2.6 ± 0.5; MTF: T0 4.7 ± 0.7 vs. T6 2.5 ± 0.5; $p < 0.01$ for each), while a significantly more marked decrease in all serum lipid parameters was observed in the PGR group as compared to baseline and to MTF, after treatment (total cholesterol, LDL cholesterol, TGs, T6 vs. T0; $p < 0.01$ for each in PGR arm vs. $p < 0.05$ in MTF arm; difference between PGR and MTF arms $p < 0.05$ in favor of PGR). Results for lipid levels are reported in **Figure 3** and **Supplementary Figure S3**, together with mean absolute values and errors bars. No serious AEs were reported in either group. Mild, non-specific AEs (such as drowsiness, reflux, headache, and dizziness) were reported in both groups in a few cases. However, significantly more gastrointestinal AEs were reported in the MTF group: tympanites (PGR $n = 3$ vs. MTF $n = 19$), flatulence ($n = 5$ vs. $n = 21$), diarrhea ($n = 0$ vs. $n = 5$), and slow digestion ($n = 1$ vs. $n = 7$).

According to these studies, in overweight or mildly obese adults, PGR treatment positively affects postprandial BG and reduces cholesterol levels as early as 1 month after treatment. Over a 6-month-treatment period, in obese adults with T2DM and MetS, the positive effects exhibited by PGR on glucose and insulin metabolism were comparable to those offered by MTF and the effects on lipid levels were better.

Preclinical Study

The only animal model study (Greco et al., 2020) evaluated the efficacy of PGR in counteracting weight gain and insulin resistance in a high-fat diet (HFD) mouse model and assessed the mechanisms underlying the favorable metabolic outcomes occurring *in vivo* after PGR. Two experimental protocols were used. In the first protocol, mice were fed either a regular diet (RD) or an HFD plus PGR or vehicle (placebo) for 2 weeks. In contrast to those on placebo, the PGR-treated HFD-fed mice displayed complete protection against weight gain, meaning that they did not show any weight gain as compared to RD-fed mice, whereas the mean body weight of HFD-control mice increased by 20% between week 4 and week 6 (10 animals per experimental group; $p < 0.001$). Moreover, since the chosen mouse strain (i.e., C57BL/6) characteristically develops marked glucose intolerance and compromised insulin response as early as within 1 week of an HFD diet, an oral glucose tolerance test (OGTT) was carried out 15 and 30 min after the glucose load, and the PGR-treated HFD mice displayed high BG peaks as experienced by the vehicle-treated HFD mice, but they reverted to baseline at 60 min, thus showing an area under the curve comparable to that of the RD-fed mice (p:ns). The second protocol investigated the ability of PGR to stop or reverse weight gain in overweight mice by feeding the animals an HFD or an RD for 4 weeks and randomizing both groups to receive either PGR or vehicle starting from week 3. During the last 2 weeks of the study, HFD-control mice continued to gain weight (a 6% increase), whereas those receiving PGR lost around 2%

of their body weight (10 animals per experimental group; $p < 0.01$). Also, the OGTT and insulin tolerance test (ITT) improved only in the latter group in which BG values remained below 300 mg/dl at 30 and 60 min after glucose load (five animals per experimental group; $p < 0.05$ for each time point) and were significantly lower than those of HFD-control mice, at 15 and 60 min after insulin injection (five animals per experimental group; $p < 0.05$ for each time point). In the same study, to explore the hypothesis that PGR could induce a specific hepatic gene expression signature, the authors investigated the circadian expression of liver genes through RNA-sequencing analysis in mice fed an HFD for 6 weeks and receiving PGR or vehicle in the last 2 weeks. Gene expression and the subsequent functional enrichment analysis showed that PGR is capable of reversing disrupted expression of several lipid metabolism–related transcription factors (TF), such as peroxisome proliferator–activated receptor (PPAR)-gamma and sterol regulatory element–binding protein (SREBP). In particular, PGR treatment downregulated the genes involved in lipid storage and induced the genes involved in insulin sensitivity as reflected by normalization (comparable to the RD-fed mice) of the glycogen and triglyceride content in the livers of the PGR-treated mice (five animals per experimental group; $p < 0.05$ for each). Furthermore, the HFD-fed mice demonstrated an impaired expression of insulin-like growth factor binding protein-2 (IGFBP-2), a protein essential to insulin action and sensitivity, which was "rescued" after the administration of PGR ($p < 0.05$).

By analyzing the composition of the experimental animals' gut microbiota (GM) through 16S rRNA sequencing, the authors also found a shift toward the enrichment of Firmicutes ($p < 0.05$) and the depletion of Bacteroidetes ($p < 0.05$) in the HFD mice, a known effect of increased HFD-driven lipid accumulation (Kojima et al., 1999; Matsuda and DeFronzo 1999; Flint et al., 2000). On the other hand, the PGR-treated mice displayed changes in GM composition that could lead to decreased energy harvest from diet.

Finally, to verify whether the effects of PGR depend on the availability of dietary components in the gut, the authors evaluated fecal nutrient excretion.

The feces from each animal were collected the day before the experiment began (Day 0), as well as on the first (Day 1) and seventh (Day 7) day of treatment and analyzed for carbohydrate and lipid levels. The PGR-treated animals displayed a significant increase in fecal excretion of lipids and carbohydrates (five animals per experimental group; $p < 0.05$ and $p < 0.01$, respectively) on Day 7 compared to the control HFD mice.

In conclusion, PGR achieved remarkable, beneficial effects on metabolic dysfunctions caused by consumption of an HFD. The mechanisms by which such effects are obtained, despite being due to sequestration, and, therefore, being non-pharmacological events elicited in the intestinal lumen, were revealed to be profound, involving a key insulin-responsive organ, and thus of systemic nature (Greco et al., 2020).

DISCUSSION

The available evidence indicates that PGR is an effective treatment in the clinical management of patients with obesity with or without established MetS, across different age groups. PGR showed beneficial effects and good tolerability also when diabetes was present, in those patients the same degree of control of glucose–insulin metabolism alterations of the standard of care (MTF) was achieved together with significantly higher lipid-lowering effects.

The available clinical data indicate that PGR, despite not having any pharmacological action, still improves MetS abnormalities. This seems to be due to a "systemic" metabolic health-promoting effect that leads to a reduced availability of carbohydrates and lipids both for the intestinal epithelia and the microbiota which positively modulates the impaired "axis" of the intestine and the organs involved in insulin response and energy metabolism and thus counteracts weight gain and insulin resistance as well as improving lipid metabolism. The biological plausibility of this "systemic" effect is supported by the data from the animal model study (Greco et al., 2020). In this study the observed favorable outcomes, including the "rewiring" of hepatic energy metabolism, were attributable to the sequestration of macronutrients by PGR in the intestine and to consequent partial restoration of the HFD-induced increase in the abundance of species belonging to the Firmicutes phylum, which have been shown to promote the absorption of dietary fats in the gut (Turnbaugh et al., 2006; Greco et al., 2020). This is consistent with studies on the relationship between gut microbiota and obesity, which have revealed important changes in the composition and metabolic function of gut microbiota in obese patients, which appear to enable the "obese microbiota" to extract more energy from the diet (Bäckhed et al., 2004; Ley et al., 2005; Turnbaugh et al., 2007; Turnbaugh and Gordon 2009). These studies have demonstrated additional interaction mechanisms with the host, including direct interaction with host epithelial cells, allowing the gut microbiota to control energy expenditure and storage (Turnbaugh et al., 2006; Petraroli et al., 2021). Thus, it is likely that the observed clinical benefit of PGR is attributable to its combined capacity to subtract energetic dietary components from intestinal absorption and, due to a change in substrate availability, to modulate the composition and function of the gut microbiota in a way that influences energy harvest from diet (**Figure 5**).

This combined capacity is in line with the reported short- and long-term positive treatment outcomes. The "immediate" effect of PGR on glucose bioavailability demonstrated in the animal study was in part confirmed in the human studies on the short-term effects of PGR administration (Belligoli and Vettor 2018) (Fornari et al., 2020) both in adults and children. In the randomized, controlled trial evaluating the single-dose effects of PGR in obese children (Fornari et al., 2020), even if the bioavailability of TGs was significantly reduced in the PGR group as compared to placebo, glucose and insulin increased similarly in both groups. According to the authors, several factors could account for the lack of effect on postprandial glucose and insulin levels, including the mixed meal administered in the study which provided a lower amount of glucose and had a lower glycemic index compared to the glucose load provided in the OGTT performed in the prior studies by Stagi *et al.* (Stagi et al., 2015; Stagi et al., 2017); the improvement of glucose–insulin metabolism reported by those studies may have been due to the effect of PGR on the anthropometric parameters over the long treatment period. The effects on the metabolic

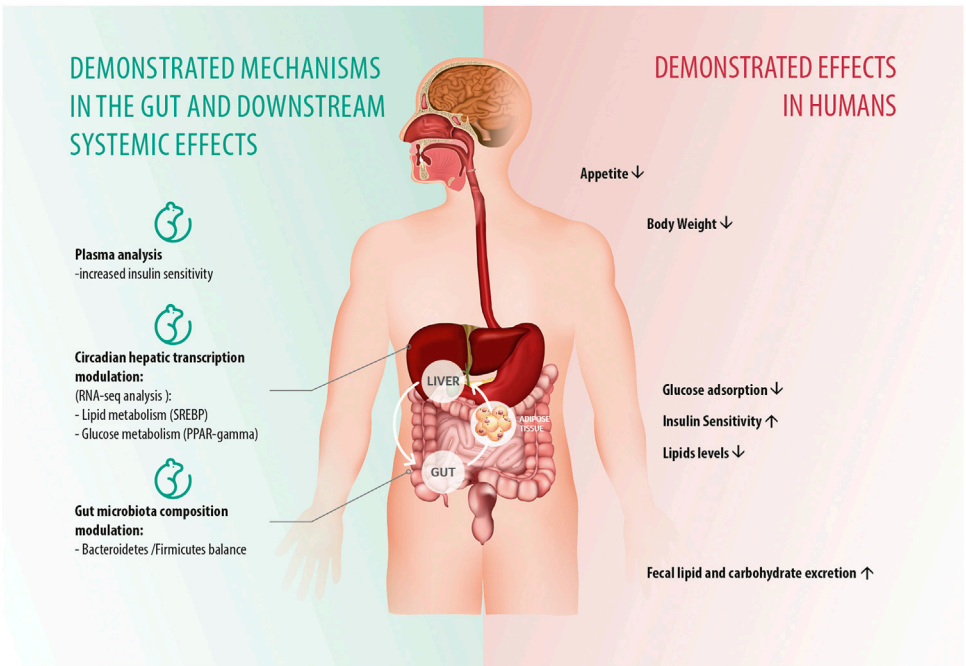

FIGURE 5 | Graphical conceptualization of PGR's translational mechanisms of action in animal experimental models and their corresponding effects in humans. Across the analyzed clinical studies (four randomized studies and one retrospective study), the addition of PGR to background lifestyle intervention achieved multiple favorable metabolic outcomes both in obese children and adolescents and overweight/obese adults. PGR decreased lipid levels in adults as early as after 30 days of treatment, while the addition of PGR significantly extended and potentiated the positive effects of MTF treatment, allowing for significant further improvement of the adiposity parameters associated with a significant reduction in glucose, insulin, and lipid alterations in obese children and adolescents with established MetS. The biological plausibility of a "systemic" effect of PGR in treated patients is supported by the data from the animal model study in which similar favorable outcomes, including the "rewiring" of hepatic energy metabolism, could be attributable to the sequestration of macronutrients by PGR in the intestine and the consequent changes in gut microbiota composition and function.

phenotype of PGR treatment observed in animals with established excess weight and glucose–insulin and lipid metabolism abnormalities were confirmed in the long-term studies in obese children and adults with and without T2DM or MetS (Stagi et al., 2015; Stagi et al., 2017). What is particularly interesting is the ability of PGR, unlike MTF, to achieve multiple favorable metabolic outcomes in adult patients with MetS and T2DM (Guarino et al., 2021): a result resembling that obtained with multiple drug treatments. In these patients, PGR displayed a significantly superior lipid-lowering capacity and similar insulin-sensitizing efficacy compared to MTF. It could be speculated that the aforementioned "systemic action" of PGR, is the driver of this beneficial effect.

Currently, MetS affects approximately 20–25% of the world's adult population in developed and developing countries (Cameron et al., 2004). In recent years, with growing rates of obesity in children and adolescents, MetS is increasingly appearing in the pediatric population. Furthermore, as suggested by the retrospective study by Stagi *et al.*(Stagi et al., 2017), non-alcoholic fatty liver disease (NAFLD) is probably more common than available studies report, even in patients not fulfilling the current criteria for MetS. For instance, a cross-sectional study evaluating the prevalence of comorbidities in school-age children with obesity found elevated liver transaminase levels in 54% of the patients (Karnebeek et al., 2019).

Even though lifestyle changes may produce significant weight reduction, the long-term efficacy of lifestyle intervention programs on BMI and the related metabolic dysfunctions is questionable, especially in children and adolescents, given the high drop-out rates from diet programs and the frequent representation of obesity in these patients (Marques et al., 2017). For this reason drugs, such as MTF, which can be used in addition to lifestyle interventions have been widely studied in clinical trials, especially in children and adolescents, and are often used in clinical practice (Wiegand et al., 2010; Brufani et al., 2013; Marques et al., 2017).

The high and increasing prevalence of obesity and MetS makes it vital to develop effective and safe therapies. Safety data for PGR are available from two studies. They demonstrate that PGR is well tolerated in children, adolescents and adults, with obesity/MetS or T2DM, also for long periods, with subsequent good adherence (Stagi et al., 2017; Guarino et al., 2021).

At present, clinical experience with PGR is limited due to the low number of studies (5 in total); therefore, more clinical studies are needed to confirm the positive results reported thus far. Other limitations must be considered when interpreting the here reviewed results, such as the quite small sample size. It is possible that other studies exist but were not retrieved because smaller studies tend to be more difficult to find. Selection criteria, especially regarding BMI, were not the same for all studies and the

duration of treatment was also markedly varied. There are no direct data regarding the efficacy of PGR compared to drugs specifically indicated for single MetS components (e.g., lipid-lowering drugs or drugs approved for weight loss).

However, the positive metabolic effects of PGR are consistent among the studies, despite their considerable differences in design and patient types. Moreover, the fact that the clinical data included in this review, with one exception, are from interventional studies merits careful consideration, as most patients were investigated within an "ideal setting", where dietary counseling (and the resulting patient adherence to the prescribed diet) was rigorously pursued. Therefore, it is conceivable that, in a real-life setting, the results attainable with a "diet-only" approach could be more modest, particularly in the long term. Finally, as already highlighted, we must consider that in pediatric and adolescent populations pharmacological approaches should be carefully evaluated because of the possibility of continuous administration for a very long period. In this context, PGR represents a valid and safe option for a non-pharmacological treatment.

The environmental effects of MTF should also be mentioned. Because of its widespread use, MTF enters the environment in large quantities, where it is partly transformed into the active contaminant, guanylurea. Both MTF and guanylurea can be detected in wastewater, plants, influents, effluents and surface waters. They accumulate in edible plants, mussels and fish, where they act as an endocrine disruptor (resulting in higher rates of intersex organisms and a reduction in the reproductive rate) and can contaminate human food (Briones et al., 2016; Elizalde-Velázquez and Gómez-Oliván 2020). This raises further concerns about increasing the use of MTF for common conditions such as obesity or MetS.

In conclusion, PGR appears to be effective in the treatment of obesity and the associated metabolic abnormalities in children or adults, even after the onset of diabetes, thus providing a non-pharmacological treatment option with a favorable risk–benefit profile for the clinical management of major metabolic derangements.

AUTHOR CONTRIBUTIONS

GG: conceptualization, methodology, validation, and writing–review and editing. MM: formal analysis, investigation, data curation, and writing–original draft preparation. FS, PM, TC, SS, and SG: writing–review and editing, visualization, supervision, and project administration.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fdsfr.2022.844256/full#supplementary-material

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Pharmacological Versus Non-Pharmacological and Ancillary Mechanisms in Eye Drops Used in the Treatment of Glaucoma

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Medical Devices Made of Substances (MDMS) are increasingly used in the healthcare system alongside classic medicinal products and constitute an important field of experimentation and innovation in the biomedical field. In fact, these products are rapidly establishing themselves as a valuable therapeutic resource and are available in various forms including, but not limited to, creams, syrups, nasal or oropharyngeal sprays, and eye drops. MDMS are marketed to treat different diseases and the advantages and benefits of the use of these products can be claimed, once proven their clinical activity. What are the differences between medicinal products and MDMS? The substantial difference lies in the mechanism of action: the first case is based on pharmacological, metabolic, and immunological actions while the second one is based on mechanical, or chemical/physical action. Sometimes the boundaries are not well defined and there is a need for a reassessment and a consensus on the underlying concepts and definitions, also in the light of the increasing ability to recognize molecular mechanisms underneath the action of several substances not acting through an easy recognizable unique target (as a receptor, for example). In the present paper, we discuss the role of eye drops as an example of MDMS used in glaucoma, a widely diffused eye disease. The choice is due to the fact that some products used in this field of application and containing similar substances are marketed either as medicinal products or as medical devices or, using other dosage forms, as food supplements. Accordingly, it is important to underscore in the various cases what may be the principal mode of action and the contribution of additional mechanisms as derived, for example, from system pharmacology data. Their analysis may help to exemplify some of the problems around the sometimes fuzzy border between MDMS and medicinal products suggesting the need for new definitions and regulatory decisions about MDMS.

Keywords: MDMS, glaucoma, mechanism of action (MOA), system pharmacology, eye drops, food supplements, medicinal product, citicoline

INTRODUCTION

Medical devices made of substances (MDMS) are health products used to cure or prevent an illness. From the patient's point of view are hardly distinguishable from conventional medicinal products and they should comply with strict regulatory definitions involving in their therapeutic action only physicochemical and not pharmacological, immunological, or metabolic mechanisms as, usually, medicinal products do.

Indeed, medical devices are vastly used in the healthcare system alongside conventional medicinal products. The EU Medical Devices Regulation (Regulation (EU) 2017/745) recently placed several devices under new classification rules (EUR-Lex - 02017R0745-20200424 - EN - EUR-Lex, 2022). MDMS are designed to treat various diseases, and patients are expected to obtain advantages and benefits with the use of these products. Clinical data are required to claim any therapeutic activity and the safety of the device should be corroborated by a post-market clinical follow-up. It should also be stressed that medical devices may be composed of substances or combination of substances which may give origin to whole body exposure (see Annex VIII of EUR-Lex - 02017R0745-20200424 - EN - EUR-Lex, 2022), going beyond the physicochemical mean thus requiring further refinement of the studies on the mechanism of action.

Even if the European regulatory constraint defines precise boundaries between MDMS and medicinal products in terms of mode of action (physical-chemical versus pharmacological, immunological, metabolic), this definition appears to be limited and insufficient to describe the increased complexity of the biological mechanisms elicited by several substances included some of those present in the MDMS. The regulatory setting is founded on the classical thinking of a pharmacological (immunological, metabolic) action, based on an easy and traceable primary hierarchically organized target and a lock-key interaction between a substance and its target. This definition is not incorrect, but it is presently insufficient to explain the biological and therapeutic effects of several substances and there is the need to expand and overcome this dated setting while defining the mode of action of a medicinal preparation, an MDMS, or, in general, a natural substance. The definition of pharmacological mechanism of action has been recently amended and further detailed in the non-binding guideline proposed by the Medical Device Coordination Group Document (MDCG 2022-5, 2022) substantially expanding the possibility to recognize a mechanism as belonging to pharmacological, immunological, metabolic domain (as in the case, for example of substances of herbal origin) when the principal mode of action is complex and difficult to define or to tribute to a specific substance. On the other hand, the same document is open to the possibility that a product containing such substances having pharmacological action could be qualified as a MDMS if the pharmacological action is ancillary to the principal intended action of the device.

In order to discuss these points, we decided to deal with a pathology, glaucoma, and a substance, citicoline, both topics on which we accumulated some direct experience in the past years.

GLAUCOMA: A RELEVANT CLINICAL PROBLEM AND AN UNMET MEDICAL NEED

It is estimated that 67 million people worldwide have glaucoma and glaucoma is the second leading cause of irreversible blindness. Glaucoma is a disease in which increased intraocular pressure is the leading cause of a subsequent degeneration of the axons of retinal ganglion cells (RGCs), which make up the optic nerve. The neurodegenerative process can progress in spite of intraocular pressure control (Davis et al., 2016). The loss of RGCs leads to loss of vision, and if untreated, to blindness (Lavik et al., 2011; Fahmideh et al., 2021). Drugs commonly used for glaucoma treatment aim to decrease intraocular pressure, mostly in form of eye drops, which, according to the clinician intention, should slow the rate of disease progression sufficiently to avoid functional impairment from the disease. Eye drops used in managing glaucoma decrease eye pressure by helping the eye's fluid to drain better and/or decreasing the amount of fluid made by the eye. Drugs to treat glaucoma are classified by their active ingredient. These include prostaglandin analogs, beta-blockers, alpha agonists, carbonic anhydrase inhibitors, and rho kinase inhibitors. In addition, combination drugs are available for patients who require more than one type of medication. An older class of medications, the cholinergic agonists (such as pilocarpine) are not commonly used nowadays due to their side effects (Weinreb et al., 2014). Considerable efforts have been made to develop neuroprotective glaucoma treatments that prevent optic nerve damage. With the development of neurotrophic, antioxidant, anti-ischemic, anti-inflammatory, antiapoptotic, and immunomodulatory therapeutic approaches, the broad field of neuroprotection in glaucoma shows progress in reducing neurodegeneration and thus stabilizing visual function in experimental studies. Unfortunately, no firm evidence exists that these agents can prevent long-term disease progression in patients with glaucoma, and still, there is a long way from basic research to the clinic (Weinreb et al., 2014; Jünemann et al., 2021). Complementary and alternative medicine is meant to be used as adjuncts to traditional therapy, including oral food supplements and MDMS (usually in the form of eye drops). It is estimated that 5–15% of glaucoma patients, reportedly spending billions of dollars annually, take some form of alternative medicine based only on their impression that it will help treat their glaucoma (John Hetherington, 2013). Nutritional supplementation comprises a broad array of products intended for ingestion to meet essential nutritional requirements. These products can be categorized as vitamins, minerals, herbals, botanicals, amino acids, fatty acids, and other dietary supplements used individually or in combination (Fahmideh et al., 2021). Regarding MDMS used in glaucoma, some of the claims lay on neuroprotection (by restoring the integrity of retinal ganglion cell membrane) and antioxidant activities including topical coenzyme Q10, citicoline, hyaluronic acid, mannitol, and vitamins B12 and E alone or in combinations. It should be mentioned that, so far, no neuroprotective drugs have been approved by the FDA and the clinical studies behind these substances are few and the majority limited to non-randomized ones.

CITICOLINE AT THE BORDER OF VARIOUS REGULATORY DOMAINS

Among the different substances, citicoline is a challenging example, worthy of attention. Indeed, citicoline has been used in several countries for several decades and, based on its properties and route of administration, this substance can be used as a drug, as a food supplement, as a food for special medical purposes, or can be dispensed as an MDMS.

Citicoline, the generic name of the International Nonproprietary Name of cytidine-5′-diphosphocholine (CDP-choline, CDPCho), is a particular molecule with psychic stimulating and nootropic activity (Adibhatla and Hatcher, 2002). In Japan and Europe, citicoline was originally used as a prescription injectable drug for the treatment of cerebrovascular and cognition disorders in people who are healing from a stroke. Nowadays, it is world widely used as an over counter dietary supplement.

Citicoline plays a vital role in the biosynthesis of phospholipids and their precursors and in maintaining the phospholipid components in the cell membranes. Its mechanism of action as well as its biological effects are multifactorial and include, but are not limited to, 1) preservation of cardiolipin and sphingomyelin; 2) restoration of phosphatidylcholine; 3) stimulation of glutathione synthesis; 4) reduction of glutamate concentration; 5) rescue of mitochondrial function, preventing neural apoptosis; 6) synthesis of myelin; 7) improvements of acetylcholine synthesis. These actions (see also Oddone et al., 2021 for a review) may lead to the prevention of endothelial dysfunction and exert a neuroprotective role of the retina (Pascale et al., 2012; Parisi et al., 2018). Thus, the neurotherapeutic effect of citicoline could be multifarious, mainly by improving neuronal membrane integrity, maintaining cellular communications with its environment, reducing oxidative stress, and improving the synthesis of neurotransmitters such as acetylcholine and dopamine. There is, in fact, evidence of a clinical effect of citicoline on several neurodegenerative diseases such as Parkinson's disease, senile and vascular dementia, and stroke (Vale, 2008; Alvarez-Sabín et al., 2013; Gareri et al., 2017; Mehta et al., 2019).

Indeed, the route of administration, dosage form, and consumption do affect its indication. When this molecule is given, it is metabolized, resulting in the production of choline. The latter is a precursor of acetylcholine, one of the most important neurotransmitters of our nervous system, involved in numerous cognitive functions, such as, for example, memory and attention (Grieb et al., 2015). In fact, nootropic substances generally carry out their actions by promoting the production of neurotransmitters, providing the body with the molecules necessary for their synthesis (Gandolfi et al., 2020).

USE OF CITICOLINE IN GLAUCOMA

Recently, due to its neuroprotective properties, citicoline has been proposed and studied as a complementary treatment of glaucoma (both as special food for medical purposes and as MDMS available as eye drops, in the latter case in association with hyaluronic acid, based on its activities in preserving the cell membrane, see below for further comments) (See **Table 1**).

Systemic Administration (as a Food Supplement or Food for Special Medical Purposes)

A recent review extensively summarized the relationship between the cholinergic nervous system and visual function and the potential implications for glaucoma neuroprotection and/or neuroenhancement (Faiq et al., 2019).

Nevertheless, in 2014, EFSA (European Food Security Authority) pronounced on the scientific substantiation of a health claim related to the new food cytidine 5-diphosphocholine and maintenance of normal vision in elderly subjects since middle age. EFSA concluded that a cause-and-effect relationship has not been established between the consumption of CDP-choline and the maintenance of normal vision; therefore, the previously mentioned health claim cannot be supported (Agostoni et al., 2014).

In the aforementioned examples the use of citicoline in symptomatic disease (glaucoma), is proposed whereas its intake by the asymptomatic general population for possible prophylaxis of this disease is not considered as supported.

Eye Drop Administration

Citicoline in eye drops can counteract the visual impairment of glaucoma (see also **Table 1** summarizing the main characteristics of clinical studies with citicoline in patients with glaucoma). Notably citicoline (2%) eye drop administration can give origin to substantial intravitreal concentrations of the compound (Carnevale et al., 2019). A study highlighted that the combination of citicoline in eye drops reduces eye pressure and slows down both anatomical and functional glaucomatous damage (Rossetti et al., 2020a). The study results showed that if glaucoma patients are accompanied by eye drops containing citicoline, in addition to ocular hypotensive therapy, the glaucomatous damage slows down significantly. Literature data show the positive effects of citicoline in glaucoma and more general in neurodegenerative diseases (Parisi et al., 1999, 2008, 2015; Ottobelli et al., 2013). It is interesting to note that in some studies (Roberti et al., 2014; Parisi et al., 2015, 2019), when glaucomatous patients were treated with citicoline eye drops, the improvement of retinal ganglion cell function (detected by pattern electroretinogram) and neural conduction along the visual pathways (detectable by shortening of visual evoked potentials) were observed. These outcomes demonstrate that citicoline not only prevents the progression of glaucoma but may assist the functional recovery of injured retinal ganglion cells as shown by recovery in the nerve signal conduction in treated patients possibly due to the RGC membrane stabilization (Parisi et al., 2015, 2019).

Once again, all the eye drops preparations containing citicoline used in these studies were medical devices and, as highlighted before, a medical device should not base its activity on pharmacological, immunological, or enzymatic

TABLE 1 | Clinical studies with citicoline in patients with glaucoma.

Product Dispensed as*	Indicated Dose and Time of Treatment	Other Active Substances Present in the Product	Study Design and Number of subjects	Parameter Measured, Comparator, and Observed Results	References
Medicinal product	1 g IM injection per day for 10 days	—	Non-randomized clinical study 30 patients (47 eyes) suffering from open-angle glaucoma	Improvement of visual fields was observed in the patients who had already taken beta-blocker eye drops. The authors suggested decreased glaucomatous optic nerve damage	Giraldi et al. (1989)
Medicinal product	1 g IM injection per day for 2 cycles of 60 days with 120 days of washout period	—	Randomized placebo-controlled clinical study. Citicoline group (n = 25) and placebo group (n = 15)	The placebo group was treated with a physiologic solution. Visual evoked potentials and pattern-electroretinograms improved in the citicoline group at different timelines	Parisi et al. (1999)
Medicinal product	1 g IM injection per day for 15 days repeated every 6 months lasted for 10 years	—	Placebo-controlled clinical study. 11 patients were treated with citicoline, while 12 patients received no treatment at all	They all had an ocular pressure normalized by topical pharmacological treatment. Citicoline administration seems to prevent the progression of perimetric deficits in glaucomatous patients	Virno et al. (2000)
Food supplement	1 g orally taken per day for 2 weeks, 2 days of washout, and repeated another 14 days of treatment	—	Non-randomized clinical study. 21 glaucomatous eyes	Improvement of visual evoked potentials in glaucomatous patients	Rejdak et al. (2003)
Food supplement	500 mg orally taken citicoline per day for 4 months, followed by a 2-months of washout, after which the therapy cycle was repeated again for another 6 months	—	Randomized clinical study. Citicoline group (n = 30) and control group (n = 30), the latter did not receive any treatment	Increased retinal nerve fiber layer thickness and ganglion cell complex thickness were observed in the citicoline group compared to the control (without citicoline) group after 12 months. The authors suggested that citicoline therapy seems to be effective in slowing POAG progression	Lanza et al. (2019)
Food supplement	500 mg orally taken citicoline per day in 2 groups: Group 1 topical IOP lowering therapy alone for the first 4 months, after which they received treatment in addition to the topical therapy for the next 4 months. Group 2 received treatment in addition to the topical IOP lowering therapy for 4 months and then continued with the topical therapy alone for the next 4 months	homotaurine 50 mg, and vitamin E 12 mg	Observational, cross over study. 41 glaucomatous patients in group 1 and 63 glaucomatous patients in group 2	A daily intake of a fixed combination of citicoline, homotaurine, and vitamin E in addition to the topical medical treatment significantly increased the total score of the contrast sensitivity test and the quality of life in patients with POAG.	Marino et al. (2020)
Food supplement	250 mg orally taken citicoline per day for 3 months and 1 month washout period	—	Randomized clinical study. 27 glaucomatous patients were in the treatment group while 27 patients were assigned to the control group	Increased inferior quadrant retinal nerve fiber layer thickness in the citicoline group at 3 months was significantly greater than in the control group. Study data show that citicoline may have a significant impact on slowing glaucoma progression, which could have a potential neuroprotective effect	Sahin et al. (2022)
MDMS Eye drops	200 mg citicoline eye drops 3 times daily for 4 months followed by 2 months washout period	Hyaluronic acid 20 mg	Randomized clinical study	Topical treatment with citicoline in POAG eyes induces an enhancement of the retinal bioelectrical responses (an increase of pattern electroretinogram	Parisi et al. (2015)

(Continued on following page)

TABLE 1 | (*Continued*) Clinical studies with citicoline in patients with glaucoma.

Product Dispensed as*	Indicated Dose and Time of Treatment	Other Active Substances Present in the Product	Study Design and Number of subjects	Parameter Measured, Comparator, and Observed Results	References
				amplitude) with a consequent improvement of the bioelectrical activity of the visual cortex	
			24 glaucomatous eyes were treated with topical citicoline, and another 23 glaucomatous eyes were only treated with IOP lowering treatment		
MDMS Eye drops	200 mg citicoline eye drops 3 times daily for 3 years	Hyaluronic acid 20 mg	Randomized, double-masked, placebo-controlled, clinical study. 40 patients were in the citicoline group whereas 38 patients were in the placebo group	Patients receiving citicoline eye drops lost lesser retinal nerve fiber layer thickness in 3 years, versus the placebo group. The authors suggest that citicoline could be a complementary treatment in the management of patients with progressing glaucoma	Rossetti et al. (2020b)

**Different commercially available forms of citicoline are present in Europe, The reported classification was done by the authors based on the route of administration and does not necessarily reflects regulatory boundaries. In the case of the Medicinal Product category it was considered that the injectable form of citicoline is approved in Europe and Japan for use in stroke, head trauma, and other neurological disorders. The use of the injectable preparation for glaucoma is experimental. Several oral preparations of citicoline alone or in combination are used as a dietary supplements with no claims allowed but their use was experimental in the quoted studies. However citicoline is also available in oral formulations as food for special medical purposes for the dietary management of patients with glaucoma pharmacologically stabilized and with progressive loss of visual field. The drop dosage form of citicoline in European countries is available and considered a medical device indicated in glaucomatous patients as coadjutant to hypotensive therapy.*
AbbreviationsIM: intramuscular; MMDS, medical devices made of substances; POAG, primary open-angle glaucoma; IOP, intraocular pressure.

properties. The view is not easy to be reconciled with the observed actions unless played exclusively at the plasma membrane level preserving its integrity.

From a more general point of view it will be important to thoroughly compare the doses used in the various studies following the different ways of administration to gain information on the citicoline eye levels when given topically and systemically.

SOME ADDITIONAL NOTES INVOLVING THE MECHANISM OF THE DESCRIBED ACTIONS AND THEIR RELEVANCE TO THE REGULATORY CLASSIFICATION OF THE PRODUCT

According to the literature data, there is the possibility that citicoline, given systemically, as a food supplement or food for special medical purposes, may act through its multiple interactions (described in the previous sections and also depicted in **Figure 1**) which do not fit the definition of pharmacological (immunologic, metabolic) mechanism because the final effect derives from complex interactions that bring about changes in a way that cannot be pinpointed at the single target/receptor level (Bilia et al., 2021).

As suggested by some of the nodes in **Figure 1** there are elements indicating citicoline involvement in glaucoma in pathways known to have an important role in neurodegeneration and apoptosis. Neurodegenerative pathways are of interest in the development of glaucoma since this condition is recognized not only as an ocular disease but also as a neurodegenerative disorder. In these years, many experimental and clinical studies have shown that in glaucoma, neuronal degeneration occurs not only at the level of the retina and optic nerve but also along the entire visual pathway and the brain.

A pathway that acts on glaucoma pathogenesis is caspase-3 (CASP3), citicoline has a potential neuroprotective effect by being involved in apoptosis through the CASP3 target and therefore management of neurodegenerative disorders. The citicoline effect is attributed to the control of neuronal apoptosis and to the induction of the regeneration of newborn RGCs neurites in experimental models including retinal explants and rat optic nerve crush model (Oshitari et al., 2010; Kitamura et al., 2019). In an *in vitro* study, citicoline administration to rat primary retinal cell cultures protected from apoptosis, by means of a reduced frequency of caspases activation and accumulation of apoptosis markers, in the presence of glutamate-induced excitotoxicity and high glucose challenge (Matteucci et al., 2014). In addition, in a recent study on a methanol-intoxicated retina model in rats, it is hypothesized that citicoline is able to minimize the loss of retinal ganglion cells and the disruption of photoreceptors, to suppress ganglion layer edema, to increase the expression of the antiapoptotic BCL-2 protein, and finally to decrease the expression of the proapoptotic caspase-3 protein (Laksmita et al., 2021).

The treatment with eye drops containing citicoline may be effective in suppressing oxidative stress and controlling inflammation in UVB corneal injury. Not only CASP3 was

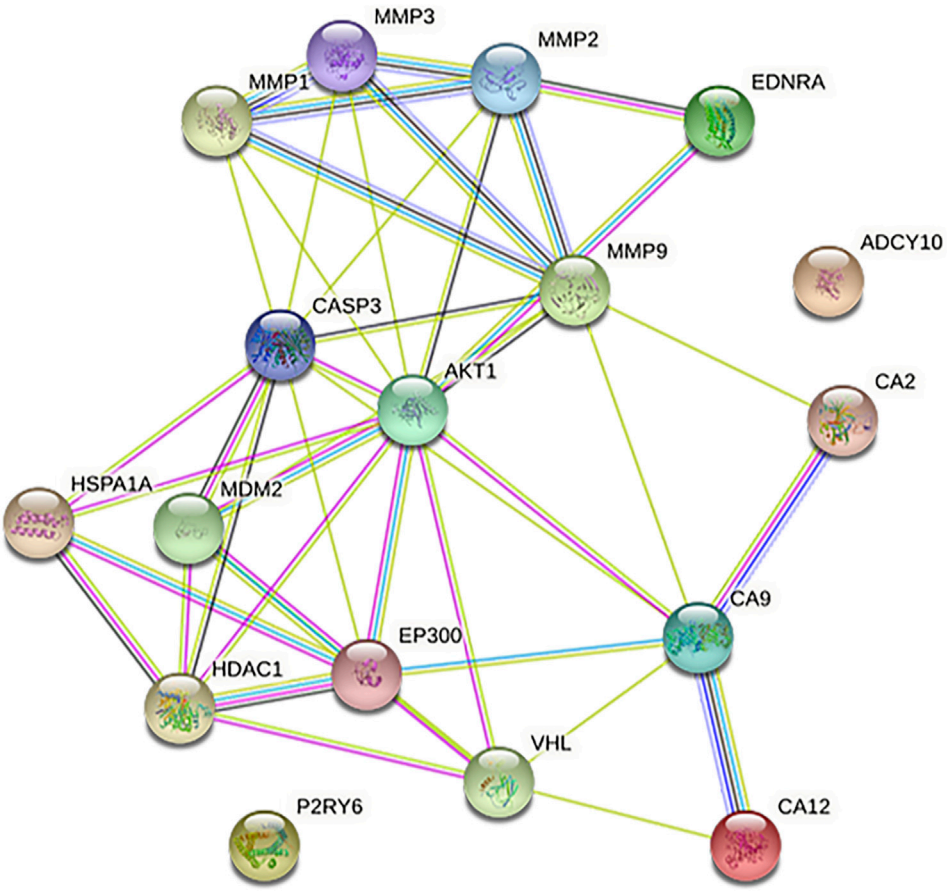

FIGURE 1 | PPI (protein-protein interaction) Network. The chemical structure of Citicoline was imported into SwissTargetPrediction data library (www.swisstargetprediction.ch) and the target of citicoline was predicted (Gfeller et al., 2014). In DisGenNet (https://disgenet.org/) the keyword of "Glaucoma" was selected to collect the targets of this disease. In order to analyze the interaction between target proteins, the targets of citicoline and glaucoma were selected and imported into the STRING database (https://string-db.org); the interactions were analyzed by selecting "Homo sapiens" as organism and setting the confidence basis to 0.4 as done by Lian and Zheng (Liang et al., 2016; Zheng et al., 2021). The image uses connectivity strength as the driving force for the layout, posing strongly connected nodes closely together, at the same time the more edge enters each node, the more involved each enzyme is in the pathogenesis of glaucoma (edges represent functional associations) (ACDY10: adenylate cyclase type 10; AKT1: protein kinase B (serine-threonine specific protein kinases); CA12: carbonic anhydrase 12; CA2: carbonic anhydrase 2; CA9: carbonic anhydrase 9; CASP3: caspase-3; EDNRA: endothelin receptor type A; EP300: histone acetyltransferase p300; HDAC1: histone deacetylase 1; HSPA1A: heat shock protein family A; MDM2: mouse double minute 2; MMP1: matrix metallo proteinase-1; MMP2: matrix metallo proteinase-2; MMP3: matrix metallo proteinase-3; MMP9: matrix metallopeptidase 9; P2RY6: pyrimidinic receptor P2Y6; VHL: Von Hippel-Lindau tumor suppressor).

evaluated but also other targets of the protein-protein interactions as Matrix metalloproteinase (MMP) −2 and −9. In particular, after immunofluorescent staining and Western blot analysis, an increased MMP-2, -9, and caspase-3 in the UVB-only group compared with the UVB/citicoline group have been shown. Citicoline treatment may be effective in suppressing oxidative stress and consequently controlling inflammation in UVB corneal injury. Citicoline exerts this effect by inhibiting lipid peroxidation and increasing antioxidant defense mechanisms (Tokuc et al., 2021).

AKT1 also is an interesting "crowded" node emerging from **Figure 1**. Indeed the PI3K/AKT pathway plays a role in neurodegeneration and in glaucoma, being involved in retinal ganglion cells and trabecular meshwork cell apoptosis, and in autophagy (He et al., 2018). However, as far as to our knowledge, there are only indirect data showing in animal studies that citicoline may act regulating such pathway in a radiation-induced brain injury rodent model (Abdel-Aziz, Moustafa and Saada., 2021).

As it emerges from the previous paragraphs citicoline has many biological interactions with cellular mechanisms. As depicted in **Figure 1** a bioinformatic analysis based on the interaction between targets of citicoline and glaucoma involved genes provides a conspicuous list of plausible targets, including some major crossroad intersections with neurodegeneration, apoptotic processes, vascular and metabolic pathways linked to oxidative stress. The questions arising are: 1) can all these nodes and putative pathways be confirmed by direct experimental data? 2) are these pathways engaged at the doses used clinically and through which route of administration? And, further, do these mechanisms fit exactly any of the present regulatory constraints to distinguish whether the product is an MDMS or a medicinal product?

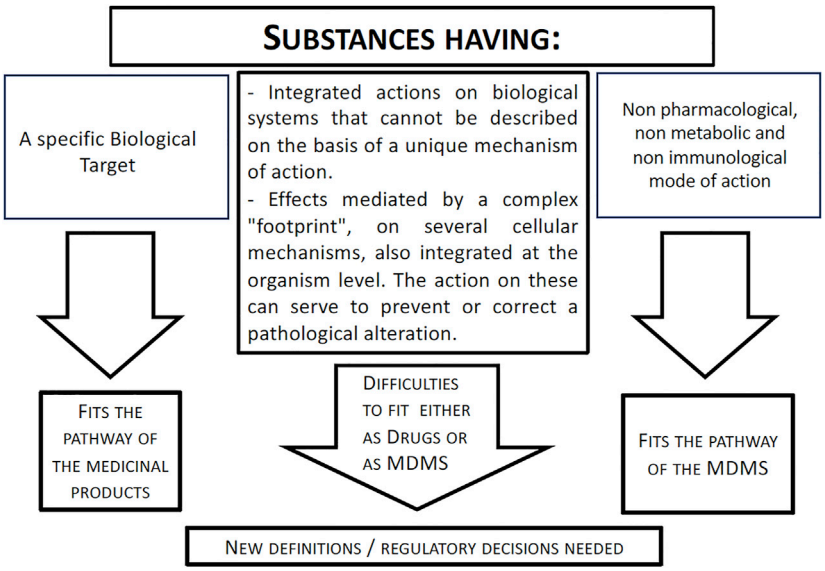

FIGURE 2 | Mode of action of a substance and relationships with regulatory pathways. The figure shows that the advancements in the knowledge of cell signaling pathways and in bioinformatics and system pharmacology have led to the understanding of novel mechanisms underlying the activity of several substances. These mechanisms do not fit the usual definitions used to classify a substance as belonging to a medicinal product or a MDMS domain. A revision of the present criteria when evaluating a mode of action of a substance integrating these new aspects may be needed. See text for further comments.

The findings of the studies briefly summarized above confirm the suggestion stemming out from the bioinformatic model involving multiple targets and a network of various correlators. The relevance of some of these targets were already suggested by clinical studies or literature searching whereas others are presently based only on bioinformatics data and are waiting for an experimental confirmation.

CONCLUSION

The case of the medical applications of citicoline and in particular of its use of glaucoma is emblematic of the difficulties of classifying some substances neatly and unambiguously as belonging to a regulatory class (medicinal product, medical device based on substances, food supplement, food for special medical purposes) (as also summarized in **Figure 2**). There are several variables including commercial choices (development investments, market access easiness, price/reimbursement) and the difficulties emerging when examining the mechanism of action of a given substance. As far as the latter point, the new investigational and bioinformatic techniques have opened to the concept of system pharmacology, which may apply to a single substance having multiple targets (as in the citicoline example) as well as to complex mix of substances, as derived from natural sources, for which is not possible to tribute the effect to a an easy and traceable primary hierarchically organized target and a lock-key interaction between a substance and its target, but rather to the resultant balanced action on multiple targets (see also Racchi et al., 2016; Bilia et al., 2021). In some cases these substances have already an history of either food or medical (albeit not registered) use in humans and a known profile of safety. Presently their development either as drugs or as MDMS is paved by difficulties and one is the discrimination between pharmacological and non-pharmacological mode of action that, as shown in the case of citicoline, may not be easy to discriminate and may differ according to associated variables such as the way of administration, the dose, the selection of a target among many possible/available. Provided the demonstration of a clinical activity consistent with the intended proposed use and the compliance to safety standards it may be proposed that such active substances, not fully complying with the present regulatory definitions concerning the mode of action, may follow either the MDMS or the medicinal product registration procedure rather than be confined to the fuzzy domain of food supplements which does not prevent their use but does not impose clinical demonstration of their efficacy and therefore, correctly, does not allow specific claims.

The way of reasoning here used for citicoline as a case study may be applied also to a mix of substances or to complex substances of natural origin at the cost of exponentially increasing difficulties because of the need to: 1) identify all the potential targets for each single molecule in study and match them with critical pathogenic biological targets/pathways underlying the disease; 2) verify to what extent each target is critical in the development/control of the disease and their hierarchical organization; 3) verify to what extent the activation and/or inhibition of the biological target

takes place at the doses/routes of administration used for the intended purposes. It has then to be decided whether these mechanisms involve specific interactions, at the molecular level, with the biological targets and whether their engagement orientates toward the classification as medicinal product or allows also the MDMS classification depending upon the use, the dose, the mode of administration. On the other hand these aspects dealing with system biology and network pharmacology are further blurring the boundaries between drugs and MDs underscoring the need to further develop the scientific debate.

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Medical Devices Made of Substances: The Need for a Change in Approach in Paediatrics

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Paediatricians are often called on to weigh up potential side effects and interferences associated with drug treatments. Ethical concerns often prevent clinical trials in children, meaning that specific data for the paediatric population can be lacking. This is true for pharmacological therapies and also natural remedies used as add-on therapy. Among natural health products are "medical devices made of substances" (MDMS) which have become increasingly important in the treatment of many disorders; the substances contained in MDMSs frequently consist of molecular structures present in a standardized preparation derived from a natural source which act as a "system." The benefits of using MDMSs to treat paediatric conditions such as gastrointestinal disorders and obesity have been proven, although there remains a degree of uncertainty about the precise mechanism of action underlying their therapeutic effectiveness. This paper argues in favour of using MDSMs when there is scientific grounds to prove their efficacy.

Keywords: medical device, medical device made of substances, paediatrics, paediatrics (drugs and medicines), children

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INTRODUCTION

Paediatricians are often called on to address questions regarding potential side effects and interference associated with drug treatments (Nakama et al., 2019).

Since the early 1960s, when it became increasingly clear that children were often "therapeutic or pharmaceutical orphans" (Wilson, 1999), there has been a growing global awareness of the need to improve the health of children by reducing the potential risks of pharmacological treatments. Medical science no longer considers children as "little adults", but as a special and very heterogeneous group of individuals (infants, for example, have very different needs and characteristics from adolescents) (Joseph et al., 2015). The diseases of childhood are different from adult diseases, and the same diseases can present themselves differently in children and adults; unlike adults, the physiological characteristics of paediatric patients depend very much on their age and stage of development (Joseph et al., 2015).

The availability of specific paediatric medicinal products is limited (Ernest et al., 2010), and data regarding dosage and efficacy in children for drugs developed for the adult population are often lacking (Klassen et al., 2009).

Given the difficulties of tailoring drugs to the needs of children, there is a high risk that therapies will be sub-optimal, unexpected responses will occur and adverse reactions and toxicity could be problems (Joseph et al., 2015). This is particularly true for children suffering from chronic diseases or with special health care needs, who are typically exposed to multiple concurrent medications in inpatient and ambulatory settings (Feinstein et al., 2014).

The discovery and use of natural remedies as add-on therapies should, therefore, be considered on the one hand with greater open-mindedness, seeking, through clinical studies as accurate as possible, to obtain proven clinical data and benefits in paediatrics; on the other hand as a potential means of reducing problems associated with traditional treatments, which are often connected to a clear key-lock mechanism (Beer et al., 2016). There is growing interest among parents, clinicians and researchers in using "natural products" for the treatment or alleviation of diseases or in association with traditional drugs to limit adverse effects. Complementary and alternative medicines (CAM) have most often been used to treat musculoskeletal problems (particularly back and neck pain), head and chest colds, anxiety and stress, and attention deficit disorder (ADHD) (Godwin et al., 2013). Complementary compounds are used together with chemical drugs in two thirds of children pharmacologically treated, in particular for upper respiratory tract infections, infant colic and other gastrointestinal disorders, and sleep disturbances, making it important to understand potential interactions with chemical drugs (Beer et al., 2016).

In the past, studies of Natural Health Products (NHPs), have led to the discovery of new drugs. Having been structurally "optimized" by evolution to serve particular biological functions (Atanasov et al., 2015; Atanasov et al., 2021), the molecules NHPs contain have a much greater scaffold diversity and structural complexity than synthetic molecules (Atanasov et al., 2015). Natural substances allow active principles to be isolated, while keeping the complexity of the starting material (Bilia et al., 2021). At present, in many European countries, numerous botanical products are present on the market as Medical devices (MDs).

MEDICAL DEVICES MADE OF SUBSTANCES

A medical device is defined as any device intended to be used for medical purposes. There are many items which fall within this definition and are used for disease management (Popov et al., 2020). In the European Union, botanical products sold as MDs are subjected to regulation by Directive 93/42/EEC and the more recent Regulation 2017/745/EC, which introduces the official term "medical devices made of substances" (MDMS) (Bilia et al., 2021), referring to natural substances composed of a large number of molecules, which act in synchrony, through a non-pharmacological mechanism of action, in a way, that is, best represented by the concept of a "system" (Bilia et al., 2021). MDMSs and medicinal products, therefore, both have therapeutic effects, although their mechanisms of action are different (Bilia et al., 2021). Medicinal products are mostly composed of a single Active Pharmaceutical Ingredient (API) and generally have one main target, whereas MDMSs, as mentioned, act in a "systemic" way (Bilia et al., 2021).

SYSTEMS BIOLOGY AND SYSTEMS MEDICINE

The concepts of "systems biology" and "systems medicine" have gained attention in recent years. Systems biology investigates biological organisms as integrated systems composed of dynamic and interrelated components (Kesić, 2016).

Living systems are immensely complicated, relying on constellations of constantly interacting networks, each of which is complex in its own right (Kesić, 2016). Systems biology has progressed rapidly in recent years due to advances in technology that enable the analysis of data from the fields of genomics, epigenomics, transcriptomics, proteomics, and metabolomics (collectively known as the "omics"). A systems approach to biology acknowledges that a molecular or biochemical factor does not act alone but is connected to many other factors (Kesić, 2016). There is a growing desire to shed light on the multiple interactive systems that are part of the complex physiological mechanisms of living organisms (Kesić, 2016). This approach is also gaining ground in paediatric care although the directions it could take are difficult to predict.

Systems medicine is an approach that uses the concepts and methods of systems biology to understand disease through an integration of data at multiple levels of biological organization (Saqi et al., 2016). An important feature of systems medicine is the interplay of biology, computation, and technology (Saqi et al., 2016). The primary goal is to improve and individualize patient care. The approach has led to the discovery that many diseases are heterogeneous and associated with several phenotypes and subtypes, each characterized by different aberrant pathways and processes (Saqi et al., 2016), which in turn has led to the development of more personalized and effective treatments, as well as subtype-specific medicines.

The past decades have seen the emergence of a new taxonomy of disease, based on molecular mechanistic features rather than the presentation of clinical symptoms (Saqi et al., 2016).

Paediatrics represents a new field in systems medicine. Novel approaches utilising cutting edge technologies are increasingly being used to identify new biomarkers which may be involved in the pathogenesis of paediatric conditions (Cheung, 2021). There have been many recent studies in paediatrics which have helped unveil more specific diagnostic markers in childhood conditions and develop more specific treatments which take into account the whole-body system (Cheung, 2021). As already specified, a fundamental concept of systems medicine is to view the human body as a network of networks. Each level of biological complexity, from genome to phenome, from cells to organ, and from molecules to individuals, can be conceptualised and modelled as networks with specific components and interactions with other networks (Cheung, 2021).

Paediatrics and its care subspecialties such as paediatric endocrinology may also be seen as component disciplines of a complex and holistic medical approach. Thinking in terms of systems can help paediatricians avoid a reductive view of disease, promote research into disease mechanisms and improve treatments. As Edgar Morin wrote in "Complexity and new science": ".....in the time of globalization, specialization guides the progress of knowledge; however, it also pushes to break down the knowledge that should be kept as a whole....." (Morin and Pieper, 1987).

It is essential to cultivate a transdisciplinary vision which places specialist knowledge in a systemic vision (Ehrich et al., 2021). Various conditions, such as, for example, altered foetal programming, can lead to disease. Maintaining a systemic vision

TABLE 1 | Data about current use of medical devices made of substances in paediatrics.

Problem/disease	References
Obesity	Stagi et al. (2015); Stagi et al. (2017); Stagi et al. (2021)
Insulin resistance and metabolic syndrome	Stagi et al. (2015); Stagi et al. (2017); Stagi et al. (2021)
Reduction of post-prandial appetite in obese	Fornari et al. (2020)
Diabetes	Stagi et al. (2015); Stagi et al. (2017); Stagi et al. (2021)
Metabolic disorders, such as dyslipidemias	Stagi et al. (2015); Stagi et al. (2017); Fornari et al. (2020); Stagi et al. (2021)
Cardiovascular diseases and hypertension	Stagi et al. (2017); Stagi et al. (2021)
Gastrointerstinal disorders (gastric pain, gastroesophageal reflux, etc)	Chellini et al. (2015); Savarino et al. (2017); Corazziari (2020)*
Acute and chronic diarrhoea	Russo et al. (2018)
Constipation	Strisciuglio et al. (2021)
Hemorrhoidal Disease	Podda et al. (2021)*
Irritable bowel syndrome	Trifan et al. (2019); Bellini et al. (2021)*
Cough and upper respiratory tract infections	Canciani et al. (2014); Cohen et al. (2017); Carnevali et al. (2021)

Data available only in adults.

which recognises the connections between childhood conditions and health in later life not only brings advantages to the individual but can also minimises healthcare costs for society (Ehrich et al., 2021).

MEDICAL DEVICE MADE OF SUBSTANCES IN PAEDIATRICS

MDMSs can bring benefits in many fields of paediatrics (**Table 1**), including in the treatment of complex conditions such as metabolic syndrome or gastrointestinal disorders.

For example, obesity, which will require huge economic resources in the future is best treated *via* a systemic approach because the pathophysiologic mechanisms underlying weight gain are much more complex and multifactorial than previously believed. It has recently been shown that polysaccharide macromolecule complexes are able to reduce plasma glucose and body weight in children and adolescents with obesity, diabetes and metabolic syndrome, opening the door to using this MDMS in association with or as an alternative to traditional drugs for suppressing appetite or contrasting insulin resistance (Guarino et al., 2013; Stagi et al., 2015; Stagi et al., 2017; Fornari et al., 2020). Indeed, treatment with this MDMS could reduce the need for treatments with drugs such as metformin which are potentially difficult to manage in children and associated with several adverse events (Stagi et al., 2017). Data for paediatric patients treated with these natural fiber complexes are similar to those for obese adult subjects (Grube et al., 2013), with a reduction in the incidence of metabolic syndrome and type 2 diabetes mellitus (Guarino et al., 2021). The MDMS was shown to significantly reduce Body Mass Index (BMI), body fat, and waist circumference, and to be non-inferior compared to metformin for glycaemic control and superior in terms of both serum lipid-lowering capacity and tolerability (Guarino et al., 2021). Ingested before meals, these macromolecular complexes can reduce the hormones that stimulate appetite as well as the post-meal triglyceride spike (Fornari et al., 2020). Importantly, they have also proved able to significantly decrease BMI and waist standard deviation score (SDS) and improve glucose control and variability in children with type 1 diabetes and metabolic syndrome (Stagi et al., 2021).

The benefits deriving from MDMS are also evident in paediatric gastrointestinal disorders, which are frequent in children and adolescents, functional constipation and diarrhoea (Russo et al., 2018; Strisciuglio et al., 2021). Moreover, although data for the paediatric population are currently lacking, in adults, the same MDMS ameliorates heartburn, gastroesophageal reflux, irritable bowel syndrome, and haemorrhoidal disease (Corazziari, 2020; Podda et al., 2021). In treating gastric acid (heartburn) or gastroesophageal reflux, MDMSs have been shown to be at least equal to drugs such as protonic pump inhibitors (Corazziari, 2020) due to their capacity to act upon pathophysiologic mechanisms that cannot be influenced by drug treatment (Corazziari, 2020). In the treatment of chronic constipation in children, MDMSs have proved as effective as oral PEG (Strisciuglio et al., 2021).

MDMSs are often used to treat coughs in children, and some data are present in the literature (Canciani et al., 2014; Cohen et al., 2017; Carnevali et al., 2021). Acute cough associated with upper respiratory tract infections is a frequent cause of distress and sleep disturbance, and the reason for many paediatric visits and drug prescriptions. MDMSs seem to be effective and safe in reducing acute and persistent cough in children, leading to a reduction in the use of specific drugs in this age group (Canciani et al., 2014; Cohen et al., 2017; Carnevali et al., 2021).

NHPs and MDMS must be subjected to the same ethical scrutiny as traditional medicines. It is fundamental that scientific data is gathered on efficacy and patient safety (Huijghebaert et al., 2020). As with drugs, treatment with any natural product must be individualized and tailored to each patient's circumstances (Huijghebaert et al., 2020). It is vital to take into account the stage of the disease, the severity of symptoms, the patient's quality of life and the existence/absence of valid therapeutic alternatives.

CONCLUSION

In conclusion, it is important to promote openminded discussion among professionals about MDMSs in paediatrics. In many ways, paediatrics can be viewed as "applied developmental biology," and paediatric diseases as occurring in systems that are still growing and developing. It has become clear that many adult

diseases contributing significantly to morbidity and mortality have their origins in childhood and early life. The challenge is to harness the potential of MDMSs in preventing and treating paediatric diseases, especially in the light of the shift towards systemic medicine. MDMSs represent a new philosophy in the treatment of diseases which employs complex substances as an alternative to or in association with traditional drugs.

It essential that we are not held back by fears or prejudices; in the words of Sir William Osler "The good physician treats the disease, the great physician treats the patient who has the disease."

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

SS conceived, edited, and approved this manuscript.

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Substance-based medical devices made of natural substances: An opportunity for therapeutic innovation

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The approval of EU Regulation 2017/745 has created a regulatory framework capable of consolidating an entire category of therapeutic products, that of Substance-based Medical Devices. The Regulation creates the conditions required to promote innovation in therapeutics, both for the so-called "minor illnesses" as well as for important "unmet medical needs". At the same time, it significantly raises the standards for evaluating their efficacy and safety. Among the different kinds of Substance-based Medical Devices, those made of natural complex substances offer a special opportunity. In this new regulatory context, natural substances can be made available to the patient within an "evidence-based" context, guided by the principles of Systems Biology and Systems Medicine, and under the control of the healthcare sector. Substance-based Medical Devices are already an important product in the European therapeutic market and will likely play an increasing role in the years to come.

KEYWORDS

substance-based medical device, medical devices made of substances, natural substances, innovation, herbal medicines, medical device regulation, mechanism of action, therapeutic effect

Introduction

The therapeutic scenario appears in continuous evolution to catch up with changes in research and development, the environment, and standards of well-being worldwide. Meeting these demands is a continuous challenge, which should take advantage in basic and medical science, technology and big data management.

There are two areas where these changes are particularly interesting:

Abbreviations: EU, European Union; MAT, Moving Annual Total; MDR, Medical Device Regulation; MP, Medicinal Product; OTC, Over-the-Counter; SBMD, Substance-based Medical Device; THMP, Traditional Herbal Medicinal Product.

1- In improving the benefit/risk ratio of current therapeutics, with a aim of minimal impact on the physiology of the whole body, especially in the long term, and on the environment.
2- In managing the complexity of new diseases and treatments: degenerative, metabolic and functional diseases, as well as multifactorial syndromes, occur at an increasingly higher frequency as the population ages (Van den Berg et al., 2006, Kelishadi 2007, Cockerham et al., 2017, GBD 2015 Obesity Collaborators 2017, DeBoer 2019, Cobiac and Scarborough 2021, Dellafiore et al., 2022, Guarino et al., 2022 (review), Nguyen et al., 2022) and often have unsatisfactory or inadequate treatments (Black and Ford, 2021; Strisciuglio et al., 2021; Bousaba et al., 2022; Negi et al., 2022; Singh et al., 2022).

The global challenges also include the so-called "minor illnesses". Lack of adequate innovation over the past 50 years has limited the therapeutic options for both patients and health professionals, calling for the development of new therapeutic approaches and solutions. All these situations may be considered as "unmet medical needs" and they will likely impact the quality of life of patients and their caregivers. Thus, it is of the utmost importance to promote innovation in patient management, in particular by promoting therapeutic products with an increasingly favourable benefit/risk ratio, especially in populations such as children, adolescents and the fragile elderly.

In this context, the Medical Device Regulation (MDR), EU Regulation 2017/745, was developed and approved by the Council and the European Union (EU) Parliament. It regulates an emerging category of products known as Substance-based Medical Devices (SBMDs). These medical devices are similar to medicinal products (MPs) in terms of their therapeutic effect and pharmaceutical formulations. However, the main difference between the two categories is that medical devices are intended for the "investigation, replacement or modification of the anatomy or of a physiological or pathological process or state" (Article 2 (1) of Regulation 2017/745), while medicinal products are used with a view to "restoring, correcting or modifying physiological functions" (Article 1 (2) of EU Directive 2001/83, as amended). Consequently, they differ in their mechanism of action: MPs have a pharmacological mechanism (acting on a specific biological target, e.g., receptors, enzymes) (Capone et al., 2012; Racchi et al., 2016) and must be able to modify a function, while SBMDs have "any mechanism that is not pharmacological (interacting with a constituent of the human body at a multifactorial and non-targeted level), and must be able to modify a process or state" (Sardi et al., 2018; Greco et al., 2020; Racchi and Govoni, 2020).

The MDR's inclusion of different type of product has created a significant opportunity for innovation. The Regulation made it possible to repurpose the therapeutic properties of natural complex substances, which were unused, or even considered as complementary and alternative medicine, within an evidence-based framework and as part of the healthcare sector.

In 2001, this issue was addressed but remained unresolved, since it classified all these products as "Traditional Herbal Medicinal Products (THMPs)". According to Article 16 of Directive 2001/83, the mechanism of action of a THMP did not need to be described and these compounds were approved for sale on the basis of a "plausible efficacy and safety", supported only by their traditional use (i.e., use within the EU for at least 15 years and in the world for at least 30 years). Even in the few cases of (very old) products authorised on the basis of their "well-established use", whose clinical efficacy could be demonstrated by published studies, the quality and mechanism of action have always been referenced to a single marker or, at most, 2–3 markers. In fact, the therapeutic use of natural substances within drug legislation required the selection of a single marker within the complex substance, and the mechanism of action and the effect of the final product had to be associated with that specific single marker. Consequently, the medicinal product legislation is not adequate to assess the value of natural substances, particularly the emergent properties deriving from their complex composition. Nowadays, this "reductionist approach" has been revised by the same regulatory agencies, since it does not reflect the real mechanism of action and cannot be established according to the rigid requirements of drug development. The ultimate price for this view is a complete lack of innovation.

Regulation 2017/745 lays out the possibility of using complex natural products and relying on "evidence-based" data, classifying these substances as complex biological substances (General Safety and Performance Requirement 13.3, Annex I of MDR). This legitimises the new criteria required to demonstrate the mechanism of action, which rely on evidence generated through Systems Biology. Through advanced techniques, it is now possible to characterize and standardize the complex mixture contained within natural products "as a whole system", without limiting its characterization to a single selected marker. This is a crucial improvement, since the standardization of a single marker cannot guarantee reproducibility between different batches of the product and, ultimately, cannot ensure the reproducibility of the benefit-risk ratio demonstrated in clinical studies. The therapeutic opportunity of SBMDs is widely confirmed by market data, which show an increasing use by patients and health professionals, and by the growing number of published clinical studies.

Substance-based medical devices: Market share

Market data can help us understand the importance of this sector both for the industry and patients.

TABLE 1 Summary of sales data showing the importance of SBMDs in the total self-medication sector, including food supplements, in some European Union Member States.

Market	Italy	Poland	Spain	France	Germany*
SBMD Market value (million €)	1,153 €	301 €	307 €	447 €	956 €
SBMD market units (million)	86	60	26	64	68
SBMD Market share value of self-medication	15.2%	9.5%	11.5%	7.0%	9.6%
SBMD value market Trend (MAT April 2022 vs. MAT April 2021)	+20%	+32%	+24%	+20%	+11%
Total Self-medication value market Trend (MAT April 2022 vs. MAT April 2021)	+13%	+21%	+19%	+10%	+13%
SBMD number of products on the market in April 2022 (launched on the market since 2016)	3,689 (1,994)	1,594 (876)	686 (415)	734 (375)	2,469 (1,239)
SBMD average price (self-medication average price)	13.33 € (12.50 €)	4.97 € (3.98 €)	11.87 € (9.44 €)	7.00 € (4.64 €)	14.09 € (10.53 €)

Source: IQVIA, Sell Out Multichannel Self-Medication Market MAT, April 2022 (* Germany MAT, May 2022).

The above data concern five reference EU countries: Italy, Spain, France, Poland, and Germany. In particular, the data regarding Italy, Germany and Poland come from data enquiries conducted on the database of the main pharmaceutical data company (IQVIA), while those regarding Spain and France come from a partial reconstruction. For these two countries the entire market of nasal saline solutions, artificial tears and eye lubricants was considered, plus individual known SBMDs (Table1).

Aggregate data for these five markets indicate that the SBMD sector is worth 3.2 billion euros, equivalent to 304 million units (MAT May 2022 for Germany, MAT April 2022 for the other countries), and has grown +18% vs. +13.5% of the total self-medication sector (including OTC drugs, medical devices, food supplements and homeopathic medicines). The number of products registered as SBMDs is greater than 9,100, of which about 4,900 have been placed on the market since 2016. This means that the companies involved in the self-medication sector are investing a lot in the development of SBMDs. This is due to the degree of innovation being delivered by these non-pharmacologically acting products as well as the approval of Regulation 2017/745, which has clarified the EU regulatory framework. SBMDs currently represent 11% of the total self-medication market, with an average price of € 10.41 vs. € 7.47 for the total self-medication sector.

Looking more specifically at the Italian market, since Italy is a European benchmark in the SBMD industry, the product category is rapidly changing the self-medication sector. As of April 2022, there are over 650 operating companies in Italy, for a market with a Moving Annual Total (MAT) in April 2022 of 1.1 billion € in value terms (31% of market share), and 87 million units in volume terms (25% of market share). The number of products classified as SBMDs has trebled since 2010, from 1,200 to 3,689 as of MAT April 2022. Of these, 1,994 products were placed on the market since 2016. Looking at the timeline, the SBMD sector is constantly growing. Notably, in 2010 it was worth € 331 million (12% of market share) almost trebling its market share. This means that three out of 10 self-medication therapeutic products sold are SBMDs. Since 2010, the growth of the self-medication sector has substantially relied on SBMDs. Interestingly, the average price of a SBMD is € 13.33, while that of the Over the Counter (OTC) medicinal products is € 12.50, implying that Patients, Medical Doctors and Pharmacists take into account the recent improvements and innovation of SBMDs and their positive benefit/risk ratio. All major multinational companies have extended their therapeutic offer through SBMDs.

In some cases, such as gastrointestinal conditions, SBMDs have grown to almost the level of OTC medicinal products: the Medical Device market share rose from 9% to 48% in sales value from 2010 to 2022. The cough market follows the same trend, increasing from a 7% market share in value in 2010 to a 24% share in 2022, especially in the pediatric population. While in 2010 the first SBMD cough syrup sold in Italy was the sixth best-selling product (Source: IQVIA Flexview Multichannel Italia - MKT Moving Annual Total Apr 2022), in 2022 it became the first. The same situation is reflected in Spain and Portugal, with a cumulative annual sales volume between the three countries of five million units.

It is evident that SBMDs are a central asset to the EU health system, and their development has made it possible to find beneficial treatments for common disturbances, addressing common and largely unmet medical needs.

Within this context, a special role is played by SBMDs made of natural substances. In Italy, as of MAT April 2022, SBMDs containing at least one natural complex substance (not an isolated molecule of natural origin but a complex matrix of plant raw materials) is approximately 50% of both the volume and value of the total SBMD market, while in 2010 it was 38% of its value and 42% of its volume, as shown in Figure 1.

Since it is not possible to describe the mechanism of action of complex substances within the regulatory framework defined by Annex I of Directive 2001/83 (as amended), the possibility of registering complex natural substances as innovative drugs is only theoretical and all new products will necessarily be

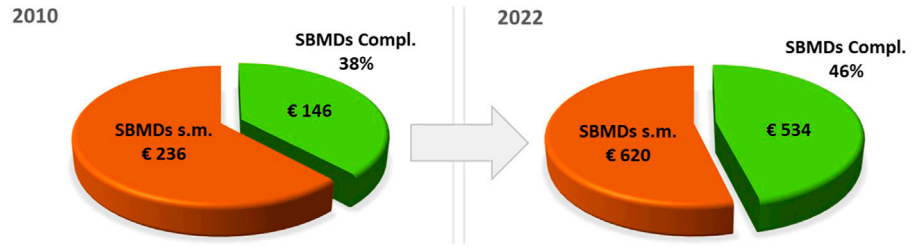

FIGURE 1
Market share of SBMDs made of natural complex substances. In Italy, the sector was worth € 146 million (38% of market share of the SBMD market) in 2010 and grew to € 534 million (46% of market share of the SBMD market) in 2022 **(A)**. Market SBMDs s.m. + SBMDs compl MAT SEPT 2010. Sell out € 382 million equal to 34 million pieces. **(B)**. Market SBMDs s.m. + SBMDs Compl. MAT APR 2022. Sell out € 1,154 billion equal to 86 million pieces. Source: IQVIA Sell Out Multichannel Market SBMD s.m. + SBMD Compl.—Sell out value (€ million) MAT SEPT 2010—MAT April 2022. SBMD s.m., SBMD made of single molecules; SBMD Compl., SBMD containing at least one natural complex component.

registered as Traditional Herbal Medicines. This problem can only exacerbate the lack of innovation in herbals containing complex substances, even in a country such as Germany whose industrial system has all the potential to perform important research and innovation in this field.

The MDR establishes a regulatory framework which allows innovation while meeting strict quality, safety and efficacy requirements and is also becoming a benchmark outside the EU. Regulations developed in Australia, Saudi Arabia, the United Arab Emirates, Morocco, Israel, Argentina, Turkey, Cuba, and Switzerland, to name but a few, have taken the EU system as their model.

Substance-based medical devices: Special provisions and global access to the market

The MDR provides SBMDs with special provisions to guarantee that only products with the highest safety and efficacy standards are marketed. In particular, the pre-marketing clinical evidence necessary to demonstrate the benefit/risk profile of devices has been significantly strengthened. All post-market surveillance and vigilance activities have likewise been improved, establishing a regulatory context which compels the manufacturer to perform a continuous and active evaluation of its products. The evaluation of clinical data, post-market surveillance and vigilance activities are not only necessary for patient safety but are also opportunities for innovation and research. The possibility of conducting interventional, comparative, often randomized clinical studies which evaluate new products versus the current standard of care, as well as the implementation of Real-World Evidence, are extraordinary and novel forces driving research and innovation.

With respect to Directive 92/43 (as amended), the MDR introduced a new classification rule, Rule 21. This rule does not include all SBMDs (for example injectables are excluded) but it regulates the SBMDs "*that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body*".

This rule significantly increases the standards required to obtain the certification of these medical devices. For example, compared to Directive 93/42, it eliminates the possibility of classifying devices in class I (which requires only a simple self-certification by the Manufacturer). This evolution is desirable, since in some cases, low quality devices or devices with no added value to the current standard of care are marketed. According to Rule 21, all SBMDs need to be evaluated by a Notified Body to guarantee efficacy, safety, and a sound benefit/risk profile.

It is worth mentioning that the first indent of Rule 21 introduces an important change into the framework of Directive 93/42: it envisages the possibility of CE marking products which should be systemically absorbed in order to achieve their intended use as SBMDs. This is a category of product that was not included in Directive 93/42 and it opens important avenues for innovation, in particular for the use of natural substances in the treatment of "systemic" disturbances such as insomnia, urinary tract infections and so on. The Regulation stipulates that these types of SBMD should be classified into the highest risk class (class III) and that a drug agency of a Member State be involved in the assessment, in addition to the Notified Body.

During the legislative process to approve the MDR, as well as during the Trilogue phase, the EU Parliament has strongly defended the entire SBMD category to encourage their development, innovation, and research. The initial MDR proposal has been extensively discussed and finally approved after 5 years. The final agreement achieved an important political compromise, offering a great opportunity to invest and develop new research trends for sustainable health.

Discussion

The new medical device Regulation provides a framework that opens up innovative treatments and ensures a positive benefit/risk profile for the products under its jurisdiction. Within the SBMD sector, there has been a particular focus on the possibility of developing new therapeutic products made of natural complex substances.

The market data, the rapid development of the scientific literature and clinical studies clearly indicate the importance and innovative value that this category of products has to offer to the European health, social and economic sectors. The demand for these products from patients and professional health care providers, including physicians, indicates that they can satisfy health needs, with a positive impact on the population's quality of life. The market data show that SBMDs are not in competition with medicinal products, but rather play a role in extending the therapeutic armamentarium with new treatment possibilities, thus broadening patients' choice.

In the sector of natural complex substances, Regulation 2017/745 opens up extraordinary opportunities for development of innovative, efficacious natural products, whose safety is important for both humans and the environment. Indeed, natural products are biodegradable due to their natural origin (EMEA/CHMP/SWP/4447/00 corr 2 2006; EMEA/CHMP/SWP/4447/00 rev.1 2018), a relevant aspect which is in line with the political, economic, and social strategies defined by the "Next Generation EU" program.

Having provided a clear regulatory framework, SBMDs, whether natural or synthetic, can be developed as safe, effective, and innovative therapeutic products, and it is necessary to implement the Regulation correctly, in order to respect the intentions of the legislator.

This involves a variety of tasks for stakeholders and Regulatory bodies:

- Industry's task is to adapt its skills to the new requirements, and to align with the challenge of increasingly innovative product development.
- The Research and Development sector's task is to continuously generate robust evidence that proves the efficacy and safety of these products. The generation of new data and the development of more specific methods of clinical evaluation to demonstrate the efficacy and safety of natural complex therapeutic products are of particular importance, to provide a sound and adequate evaluation of risks and benefits as required by Regulation 2017/745 on SBMDs.
- The task of the Regulatory bodies is to effectively implement the Regulation. This means an end to the restrictive attitude that systematically classifies any product with a therapeutic activity as a medicinal product regulated according to the Directive 2001/83 Article 2 (2). On the contrary, medical device and medicinal product legislation should be developed as two coordinated systems that jointly aim to guarantee the widest spectrum of treatment choices and safety for the patient. More specifically, pharmaceutical legislation can continue to be the normative frame of reference for cases in which the therapeutic activity is entirely and exclusively ascribable to a specific molecule contained within it, while the SBMD framework should be taken as the reference when the action is linked to the emergent properties of the entire complex natural system. In the former case, in fact, the mechanism of action can be developed within a pharmacological context (up to the purification of the active molecule), while the latter remains within an evidence-based framework but one that is oriented to the principles of Systems Biology.

Failure to do so would result in harm to EU patients, since it is known that the characteristics of these products, which are intended to have a therapeutic effect by targeting "a physiological process or state" through a "non-pharmacological" mechanism of action, could no longer be registered as drugs. It is therefore not a question of whether these products should be classified as drugs or devices, but whether we want to support or prevent the development of effective and safe new treatments for humans and the environment. If this developmental roadmap is followed, it will create opportunities for everyone; if it fails, these products will be narrowed and limited to the realm of alternative medicine, with major safety and social consequences.

We are witnessing the rise of new types of products, new research patterns, and a significant expansion in the therapeutic tools that are accessible to all, and for the benefit of all.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions. We carried out queries against payment on a professional data set (IQVIA), cited when necessary, especially on each caption. Requests to access these datasets should be directed to Sofia Musella, smusella@aboca.it; Enrico Novelli, enovelli@aboca.

Author contributions

EG conceived and wrote the manuscript.

Conflict of interest

Author EG is a member of Confindustria Substance-based Medical Device Group and is employed by Aboca S.p.A.

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Corrigendum: Substance-based medical devices made of natural substances: An opportunity for therapeutic innovation

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A Corrigendum on
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In the published article, there are some errors in Table 1 as published. One error is the percentage in the second column third line and the other one is the price in the second column last line (1.50 €), both referred to Italy. The third error is the price in the third column last line (3.97 €) referred to Poland. Other numerous errors were found in the "France" column, the entire column. The last error is in the caption where the word "total" is missing.

The corrected Table 1 and its caption appear below.

In the published article, there were some errors in the following paragraph that contains data related to Table 1.

The corrections have been made to **Introduction** in the paragraph ***Substance-based medical device: Market share***, page 03. These sentences previously stated:

"Aggregate data for these five markets indicate that the SBMD sector is worth 2.9 billion euros, equivalent to 270 million units (MAT May 2022 for Germany, MAT April 2022 for the other countries), and has grown +19% vs. +13.5% of the total self-medication sector (including OTC drugs, medical devices, food supplements and homeopathic medicines).

The number of products registered as SBMDs is greater than 8,700, of which over 4,600 have been placed on the market since 2016. This means that the companies involved in the self-medication sector are investing a lot in the development of SBMDs. This is due to the degree of innovation being delivered by these non-pharmacologically acting products as well as the approval of Regulation 2017/745, which has clarified the EU regulatory framework.

SBMDs currently represent 10% of the total self-medication market, with an average price of € 10.86 vs. € 7.47 for the total self-medication sector."

TABLE 1 Summary of sales data showing the importance of SBMDs in the total self-medication sector, including food supplements, in some European Union Member States. Source: IQVIA, Sell Out Multichannel Self-Medication Market MAT, April 2022 (* Germany MAT, May 2022).

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IQVIA, Sell Out Multichannel Self-Medication Market MAT, April 2022 (*Germany MAT, May 2022).

The corrected sentences appear below

"Aggregate data for these five markets indicate that the SBMD sector is worth 3.2 billion euros, equivalent to 304 million units (MAT May 2022 for Germany, MAT April 2022 for the other countries), and has grown +18% vs. +13.5% of the total self-medication sector (including OTC drugs, medical devices, food supplements and homeopathic medicines). The number of products registered as SBMDs is greater than 9,100, of which about 4,900 have been placed on the market since 2016. This means that the companies involved in the self-medication sector are investing a lot in the development of SBMDs. This is due to the degree of innovation being delivered by these non-pharmacologically acting products as well as the approval of Regulation 2017/745, which has clarified the EU regulatory framework. SBMDs currently represent 11% of the total self-medication market, with an average price of € 10.41 vs. € 7.47 for the total self-medication sector."

The author apologizes for this errors and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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European Union Regulation on clinical trials and Regulation on medical devices: A common soil for future development

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The recent European Union (EU) Regulations on clinical trial on medicinal products (MPs) (2014/536) and on medical devices (MD) (2017/745) represent potential improvement for the European health system and may offer advantages to the citizens. As Regulations, they are immediately applicable in Member States overruling national laws, being an advantage for stakeholders (e.g. sponsors and investigators) and Europe becomes *de facto* one homogeneous place for research and development of medicines and medical devices. This perspective commentary focuses on the most relevant methodological and regulatory aspects of the recent Regulation on clinical trials for drug development and how it may indirectly impact on substance-based medical devices (SBMD). The article highlights the innovations associated with the 2017/745 Regulation, especially to the area of SBMD, which represent a novelty among MDs. Since SBMDs share some aspects of medicines, they will increasingly undergo research in the future related to the performance and safety claims, *via* post-marketing surveillance. Importantly, SBMD's Consumers are rapidly increasing due to their usage to treat some common symptoms, which not necessarily need conventional medicines. "Frontiers in Drug Safety and Regulation" created a section to reflect this rapidly-changing scenario and host reports on SBMD in a scientific environment. This initiative is also a reflection of the recent regulation on SBMDs. Thus, the improvement of clinical research through the new EU Regulation on clinical trials may become useful also to the new requirements for SBMD. A novel editorial initiative will further contribute to implement the EU Regulation providing adequate scientific dissemination.

KEYWORDS

medical device, medicinal product, European Union Regulation, safety, performance, clinical trial, substance-based medical device

Introduction

The European Union (EU) Regulation 2014/536 on clinical trial on Medicinal Products (MPs) for human use (European Commission, 2014) and the EU Regulation 2017/745 on Medical Devices (MDs) (Eur-lex, 2018) represent two very important novel improvements for the European health system and for all European citizens under many aspects.

First they are both Regulations and not Directives: a "Regulation" is a binding legislative act, that is immediately and fully applicable in all Member States overruling the national laws. On the contrary, a "Directive" is a legislative act setting objectives that all EU countries must reach and implement into their national legislation within a defined timeframe (European Union, 2022). Thus, the Regulations represent the fastest way to modify the legislation in all European countries, representing a big advantage for all the stakeholders (sponsors, and clinical investigators for the clinical trials Regulation; manufacturers, Notified Bodies, and all the other actors for the medical device Regulation). Consequently, they will operate under the same rules in all the EU nations, making *de facto* Europe a big and homogeneous country for clinical research in the field of MPs and for the whole sector of MDs including research and development.

Such a condition will likely turn into a relevant advantage also for the EU citizens, who will benefit of new and effective treatments that will be likely available in a faster way.

The objective of this perspective commentary is double: 1) To focus on the most relevant methodological and regulatory aspects of the Regulation on clinical trials on medicinal products (MPs) in the EU and how it may indirectly impact on the sector of Substance-Based Medical Devices (SBMDs) and 2) To highlight the innovations that the EU Regulation 2017/745 could specifically bring to the field of SBMDs.

The possible advantages that can be expected for the health of the individual citizen, either as consumer of SBMDs or as patient will be briefly summarized.

The emerging and relevant problem associated with the pollution caused by pharmaceuticals, given that the emissions of substances used for therapeutic purposes into the environment occur during their whole lifecycle, i.e., from production through consumption to disposal (European Commission, 2013; COM, 2019), will not be discussed in this paper even if a positive impact of MDs that are based on natural substances could be expected.

The European Union Regulation on clinical trials: Methodological and regulatory aspects

The EU Regulation 2014/536 on Clinical Trials on medicinal products for human use has entered into application on 31 January 2022. A work plan has been recently released (EMA, 2022) to complete its implementation.

There are many reasons for developing this Regulation in the EU. Certainly, a major driver was to make EU attractive and favorable for performing large interventional trials with high standards of public transparency and safety for their participants. In other words, Europe has been trying to set the stage to be competitive and attractive to host large, homogeneous and innovative clinical research and development as a whole country, as opposed to nations as China or Brazil for example, which due to their population size represent major competitors.

Leading quality in clinical research is central to the proper growth of the health system as a whole, and it is a driver for the economic development of each EU country. Thus, by supporting and regulating the conduct of large clinical trials in all EU member States, Europe aims at attracting large investments. At the same time, promoting medical innovation would benefit all patients by increasing the number of new and innovative available medicines.

Randomized clinical trials (RCTs), possibly based on a hypothesis of superiority, are indeed necessary and required to generate the highest quality of the evidence regarding the efficacy and safety of all healthcare interventions. Both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) rely on RCTs to reach a decision on the authorisation of new medicines**.** Although the use of placebo has long been debated, placebo as control in RCTs can establish the assay sensitivity, i.e., the ability to discriminate whether a treatment is really effective (Temple and Ellenberg, 2000). However, RCTs may also need to compare efficacy and safety of new treatments against existing active alternative of care proved to be effective by previous studies against placebo. Since high quality RCTs provide the best evidence for developing international guidelines worldwide, it seems important to increase the use of the best active or gold standard comparator(s), when available, for the specific disease treated in the specific RCT dealing with medicinal products (Naci et al., 2020). The new EU Regulation may endorse quality in RCTs, supporting RCTs of superiority of new treatments *versus* the available standard of care, rather than *versus* placebo.

Without doubts, patients are the fundamental partners in the generation and appraisal of relevant and trustworthy evidence from RCTs (Greenhalgh et al., 2019); their recruitment and retention during the entire RCT have become a major challenge for those running RCTs, likely because of a reduced confidence or poor awareness of patients in the cornerstone value of clinical research. Thus improving the quality of RCTs may help increasing patient's participation. In fact, the Regulation 2014/536 clearly states that in a clinical trial the rights, safety, dignity and wellbeing of subjects should be protected and the data generated should be unbiased, reliable and robust. The interests of the subjects should always be the main priority overcoming all other interests.

TABLE 1 Medical device regulation in the EU and in the United States (modified from Naci et al., 2020).

	EU	United States
Regulatory Agency Statement	There is no centralised agency responsible for regulating medical devices in Europe; for medical devices, private and for-profit notified bodies designated by national competent authorities are responsible for conducting conformity assessments; a medical device can be marketed in the EU either after self-certification by the manufacturer for some low-risk devices (class 1) or after receiving the certificate of conformity by a notified body; the Conformité Européenne marking is affixed by the manufacturer to confirm that it has a certificate; EMA's regulatory role is primarily limited to medicinal products that include a medical device (combination products, medical devices with an ancillary medicinal substance, companion diagnostics used to identify suitable patients for treatment, and medical devices made of substances that are systematically absorbed)	The FDA is responsible for regulating medical devices in the United States; a medical device can only be marketed in the United States after receiving FDA approval

The COVID-19 pandemic has made this issue even more important and other ways to run RCTs have been suggested such as Decentralized (Goodson et al., 2022) or *in silico* (Pappalardo et al., 2019) RCTs.

A major aim of the Regulation is to foster innovation capacity of the European medical research, at the same time protecting public health and recognizing the legitimate economic interests of the sponsors. Thus, it clearly appears that a significant advantage of the clinical trial Regulation is for the patients who would prefer to be recruited in relevant RCTs and for the citizens at large who could benefit of new, safe and more effective medicines. This may contribute to ameliorate the health system due to a better investment of public and private resources.

The new Regulation on clinical trials on medicinal products for human use will likely positively impact on the clinical investigations involving medical devices and particularly those on medical devices based on substances as described below. Better conduct of clinical trials for MPs will be a reference quality in supporting the research for the claims of performance of many SBMDs used in common functional symptoms. In fact the Regulation on MDs has taken up many aspects of the regulatory framework on pharmaceuticals in relation, for example, to ethical aspects and to the quality of studies.

The European Regulation on medical devices: Focus on substance-based medical devices

The definition of Medicinal Product (MP) and of Medical Device (MD) is reported in one of the other three Perspective Articles that have been invited and published for the Research Topic: Medical Devices made of substances for human health: a challenge in terms of efficacy, safety and sustainability (Leone, 2022).

Basically, Medical Devices are products or equipment intended for a medical purpose. If they are composed of substances or combination of substances, they are defined as *substance-based medical devices* (*SBMD*).

The EU Regulation 2017/745 (Eur-lex, 2018) on medical devices (MDR) has introduced several relevant novelties, reducing the gap of information necessary at the time of their CE mark in comparison with the data requested for the marketing authorization of pharmaceuticals. It also requires to promote post-marketing clinical follow up studies in order to increase availability of data supporting their performance and safety. Overall MDR increases the clinical informations necessary to obtain the CE mark from the Notified Bodies and promotes post-marketing studies to confirm the positive benefit-risk balance over time during marketing.

By introducing a new international Unique Device Identification (UDI) system and a publicly accessible European database (EUDAMED), traceability and transparency of MDs will be likely increased (Antich-Isern et al., 2021). The MDR mirrors the regulatory scenario of medicinal products for some relevant aspects, such as the continuous evaluation process of the post-marketing benefit-risk profile. The pre- and post-marketing clinical research of MDs will certainly indirectly benefit from the Regulation on clinical trials of medicinal products in terms of quality of the studies and comparative approach. An increase in studies *versus* active-comparator rather than *versus* placebo can be foreseen.

This is particularly true for the sector of SBMDs, whose existence is formally acknowledged by MDR (rule 21).

At a first glance of the MDR, SBMD may appear handled similarly to medicinal products (MPs) since their claim is to have a therapeutic effect and the formulations are similar to those of MPs. In particular, the definition of risk class III SBMD as reported in the Rule 21 first and second indents of the Regulation (EU) (Eur-lex, 2018), states that the intended use of MDs is very similar to MPs (Leone, 2022):

Devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body are classified as:

1) class III if they, or their products of metabolism, are systemically absorbed by the human body in order to achieve the intended purpose;
2) class III if they achieve their intended purpose in the stomach or lower gastrointestinal tract and they, or their products of metabolism, are systemically absorbed by the human body.

As recently reviewed (Fimognari et al., 2022; Leone, 2022), MPs and SBMDs however differ in their mechanism of action: MPs have a demonstrated pharmacological mechanism of action while SBMDs must have "any mechanism, that is, not pharmacological". The definition of a "non pharmacological" mechanism of action for a therapeutic product represents a big challenge for preclinical and clinical research.

Moreover the reference to Annex I of Directive 2001/83/EEC increased the level of preclinical and clinical data for SBMD as reported in the MDR: *Devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body, and that are absorbed by or locally dispersed in the human body shall comply, where applicable and in a manner limited to the aspects not covered by this Regulation, with the relevant requirements laid down in Annex I to Directive 2001/83/EC for the evaluation of absorption, distribution, metabolism, excretion, local tolerance, toxicity, interaction with other devices, medicinal products or other substances and potential for adverse reactions, as required by the applicable conformity assessment procedure under this Regulation.*

It must be noted that the regulatory marketing process of MDs is different in the EU and United States as reported in Table 1, with a different role of regulatory agencies.

While in the United States a MD can be marketed only after FDA approval, in the EU the situation is more complex.

EMA opinion, which is not binding, is requested only for class III SBMDs reported in the first indent of Rule 21, i.e., those that are systemically absorbed by the human body in order to exert a therapeutic effect (or in order to achieve the intended purpose as reported in Rule 21). A proper implementation of the MDR will require harmonization and collaboration of competent authorities. For more details see Leone, 2022.

The market of SBMDs is increasing in the recent years, currently representing 10% of the total self-medication market in the European countries (Giovagnoni, 2022). With the full implementation of the MDR (Eur-lex, 2018), an increase in preclinical and clinical studies will likely occur. SBMDs largely address medical needs such as common diseases where the pharmacological treatment could be safely and effectively replaced by a SBMD. For example, in the pediatric population, a SBMD made of natural fiber complexes was shown to significantly reduce Body Mass Index, body fat, and waist circumference and to be non-inferior to metformin for glycaemic control and superior in terms of both serum lipid lowering capacity and tolerability (Guarino et al., 2022; Stagi, 2022). Thus it will necessary to produce comparative evidence of SBMDs *versus* the MPs used in a specific clinical setting. The comparative evidence should come from studies performed before and after CE mark. Comparative research could represent the best way to increase the public trust in clinical research and to pave the way to a more personalized medicine (Singh et al., 2020).

Conclusion

The Regulations concerning clinical research of MPs and the more general regulatory framework of MDs, and in particular SBMDs, in the EU have recently undergone parallel major revisions, in the interest of the wellbeing of the citizens, of the quality of science, and of improving feasibility and homogeneity among nations.

In particular, SBMDs which share several aspects with MPs, will increasingly undergo processes of research and development in the near future, regarding the claims of *"effectiveness"* and the post-marketing surveillance for safety. Both assessment of effectiveness and safety of SBMD can use the guidance developed for MD or drugs by Regulations on clinical trial on MPs (2014/536) and on MD (2017/745). Importantly, the market of class III SBMDs is undergoing a fast rise, filling some gaps and unmet medical needs in the treatment of common symptoms which not necessarily need pharmacological agents.

For all the above reasons, the section on SBMDs as a separate part of the Journal "Frontiers in Drug Safety and Regulation" has been created to reflect these rapidly changing developments and to host reports and debates on SBMDs in a scientific, high quality editorial environment. This initiative also reflects the spirit of the recent regulation on SBMDs that requires to continuously provide evidence of their safety, and to strengthen their claims of *"effectiveness"* with a methodologically rigorous and scientific approach. This novel editorial initiative will further contribute to implement the EU regulation at the level of the scientific dissemination.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Gastrointestinal functional disorders can benefit from the use of medical devices made of substances

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Medical devices made of substances (MDMS) have recently gained great popularity in several specialties of internal medicine, including gastroenterology. In the last decades this discipline has known relevant advances in the cure of severe diseases, such as peptic ulcer, gastroesophageal reflux disease and chronic hepatitis C, thanks to the revolutionary development of new drugs able to act on single receptors changing a particular cell function or blocking microbial and viral replication. However, there are many gastroenterological illnesses that are difficult to treat with traditional medicinal products because of their complex and poorly known pathophysiology, which comprises altered motility, visceral hypersensitivity, gut dysbiosis, intestinal mild inflammation with impaired immune function, increased mucosal permeability and abnormal brain-gut interaction. They are mainly represented by esophageal functional disorders (reflux hypersensitivity, functional heartburn), functional dyspepsia, irritable bowel syndrome, functional constipation and functional diarrhea. Traditional drugs do not provide a definitive resolution of these disorders with a multifactorial pathogenesis and they can benefit from the use of MDMS, which seem to have the ability to act on different factors thanks to the synergistic action of their various components. International medical literature already reports many clinical trials performed with the well-known standards for evaluating their efficacy and safety in a great part of the above-mentioned conditions.

KEYWORDS

pharmacological agents, reflux hypersensitivity, functional dyspepsia, irritable bowel syndrome, medical devices made of substances

1 Introduction

Medical devices made of substances (MDMS) have gained great popularity in last years and have contributed to enlarge the therapeutic armamentarium in many internal medicine disciplines, including gastroenterology. They differ from medicinal products because their action is not characterized by pharmacological, immunological or metabolic means (Bilia et al., 2021). Despite this negative definition, MDMS are intended to have a therapeutic effect due to unknown mechanisms that need to be defined as clearly as possible. This effort requires the combined collaboration of pharmacologists, clinicians and regulators in order to

ensure the clinical use of these products within the strictest safety and the objective evaluation of their efficacy (Racchi et al., 2016).

(Racchi et al., 2016) report that the principal action of a MDMS is typically fulfilled by non-pharmacological means, such as physical means, including mechanical action, physical barrier lubrification and support to organs or body functions, or chemical means, such as pH modifications or any other acid-base reactions and chelation. These compounds often may have more than one non-pharmacological mechanism of action concurring to the claimed therapeutic effect. In fact, MDMS have the specificity of being composed of a very high number of molecules, acting in synchrony, in a way that is best represented by the concept of system, that is its effect depends on the inter-actions and inter-relations among each molecule rather than on a simple sum of its components. In other words, the mechanism of action of MDMS is linked to the entire product and not to one selected single component of it.

The Regulation 2017/745, issued by the EU parliament and the Council (Regulation (EU), 2017) states that MDMS need to be absorbed in order to achieve their intended action and this renders them similar to medicinal products, although their mechanism of action is different. Indeed, they do not act on a single pharmacological target that permits to change the function of a given cell, but may equally play an important therapeutic role in the healthcare system because there are still many illnesses with a relative low grade of risk and not responding adequately to traditional drugs. These conditions impair greatly the patients' quality of life, are frequently shared by many people and their clinical behavior is characterized by a chronic evolution with alternate phases of exacerbation and remission.

The discipline of gastroenterology comprises many disorders of this type that cannot be controlled by medicinal products and might benefit from the use of MDMS, as already shown by a certain number of well-designed and randomized studies of efficacy published in international medical literature. On the other hand, the continuous scientific advances in therapy over the last decades have allowed us to cure definitely important and severe diseases in the area of gastroenterology and hepatology. In order to understand better the difference between traditional medicinal compounds and MDMS in our specialty, it would be useful to show some of the excellent results obtained with the former drugs and the potential therapeutic opportunities of the latter in several conditions poorly controlled by pharmacological agents.

2 The revolutionary discoveries in the field of gastroenterology

2.1 Antisecretory drugs

The better knowledge of the physiological regulation of acid secretion by the gastric parietal cell has led to develop powerful pharmacological agents able to block the production of acid and to control the so-called acid-related diseases, mainly peptic ulcer and gastroesophageal reflux disease (GERD).

The development in the 1970s of H_2-receptor antagonists provided incontrovertible evidence for the importance of endogenous histamine in the physiological control of gastric acid secretion (Black et al., 1972) and transformed the treatment of the above-mentioned diseases of the upper digestive tract. These drugs inhibit gastric acid secretion elicited by histamine in a dose-dependent manner and their action is maximal in basal (fasting) and nocturnal acid secretion (Savarino et al., 1988).

Later, at the end of 1980s, more powerful antisecretory agents were synthesized, the inhibitors of H + K + -ATPase (PPIs), which is the proton pump located in the apical membrane of the parietal cell and is the ultimate mediator of gastric acid secretion (Shin and Sachs, 2009). Also the pharmacological effect of PPIs is dose-related, but is more evident during the daytime, when acid secretion is stimulated by meals than during the nocturnal periods (Savarino et al., 1998). The duration of acid inhibition is longer-lasting than that of H_2-blockers and this results in a more effective healing of both peptic ulcer and reflux esophagitis (Walan et al., 1989; Savarino et al., 2009).

More recently, a new class of antisecretory drugs, the potassium competitive acid blockers (pCABs), has been introduced into the market and they are characterized by a better pharmacokinetic and pharmacodynamic profile than PPIs (rapid onset of action, longer-lasting acid suppression and better control of nocturnal acidity) (Savarino et al., 2022). They are not pro-drugs that need to be activated in the canaliculi of oxyntic cells, like PPIs, and therefore their effect is rapid and evident within the first day of administration (Sakurai et al., 2015). Their antisecretory action relies on the inhibition of the proton pump by reducing K+ availability for the enzyme, which is essential for the maintenance of acid secretion (Abdel-Aziz et al., 2021).

From a clinical point of view, pCABs have the potential to improve the management of patients with acid-related disorders, including peptic ulcer and GERD because of their ability to overcome several important drawbacks of PPIs (slow onset of action, the scant effect on nocturnal acidity) and their action is not affected by genetic polymorphism, especially in Asian populations (Martinucci et al., 2017).

Overall, all the antisecretory agents developed in the last decades have a specific pharmacological action on a single target able to change the function of the gastric parietal cell in the production of acid and this has allowed us to cure the diseases due to acid hypersecretion and to subtract thousands of patients to the need for surgical therapy.

2.2 *Helicobacter pylori* infection

The discovery of *H. pylori* infection in the stomach has led to a major revolution in the science and practice of gastroenterology (Malfertheiner et al., 2022). Many studies have clearly shown that this germ is the major cause of gastritis and peptic ulcer, which have to be considered as infectious diseases that must be cured with antibiotics and no more with acid suppressants (Fock et al., 2013).

The most compelling evidence that *H. pylori* was indeed the main cause of peptic ulcer disease came from clinical trials because the eradication of the bacterium resulted in resolution of this disease that does not recur and is no more associated with dangerous complications, such as bleeding and perforation (Hopkins et al., 1996). Single agent therapy has proven ineffective *in vivo* and has led to the emergence of resistant strains, while double antibiotic therapy

in combination with antisecretory drugs (triple therapy) has resulted successful to heal peptic ulcer (Bazzoli, 1996). Amoxicillin and clarithromycin have been the mostly recommended antibiotics in various eradication regimens (Mégraud, 1995). The former is a penicillinase-susceptible semi-synthetic penicillin and its antimicrobial activity consists in the inhibition of the cell wall transpeptidase and is bactericidal, while the latter is usually bacteriostatic and inhibits protein synthesis by binding reversibly to the 50S ribosomal subunit of sensitive micro-organisms (al-Assi et al., 1994).

Overall, the specific action of the two antibiotics on the essential structures of the bacterium with the block of their replication is the single mechanism responsible for the success of anti-Helicobacter therapy.

2.3 Chronic hepatitis C

Finally, an additional example of revolutionary therapeutic success is the development of powerful antiviral drugs, which have allowed us to cure a dangerous and severe disease, such as chronic hepatitis C, which is able to evolve to cirrhosis and hepatocarcinoma in many cases (Huang and Yu, 2020). In fact, the virus responsible for this disease (hepatitis C virus = HCV) can be eradicated virtually in all patients with short courses of the new direct-acting anti-viral agents (DAAs), generally from 6 to 24 weeks (Chhatwal et al., 2015).

The selection of the most convenient DAA regimen is firstly driven by the HCV genotype. If it is true that HCV elimination is immediately associated with liver improvements, halting and reversing hepatic fibrosis, also direct extra-hepatic complications of HCV replication, including mixed cryoglobulinaemia vasculitis, resolve after HCV eradication in most cases (Soriano et al., 2016). In addition, indirect extra-hepatic damage as result of persistent systemic inflammation ameliorates following HCV cure with improvements in diabetes, dyslipidemia and fatigue, along with a reduced incidence of cardiovascular events, renal disease and lymphomas (Negro and Hepatitis, 2013).

For instance, (Foster et al., 2016), using sofosbuvir combined with velpatasir, were able to eradicate HCV in more than 90% of their patients with HCV genotype 3 infection, which is the most difficult form to cure, and obtained 100% eradication in patients with the other genotypes after 12 weeks of treatment.

Once again, these excellent results in the therapy of HCV infection were due to the clinical use of DAAs, which are antiviral drugs acting as protease or polymerase inhibitors and then permit to block HCV replication with a single and precise mechanism of action (Ford et al., 2014).

3 The large body of functional disorders in gastroenterology

If the use of revolutionary pharmacological agents has allowed us to change dramatically the natural course of some important digestive and hepatic diseases, such as GERD, peptic ulcer and chronic hepatitis C, there are several other illnesses that affect many patients in the field of gastroenterology. They do not have a structural basis to explain their clinical features, which are generated by a complex interaction among various factors such as microbial dysbiosis within the gut, altered mucosal immune function, altered gut signaling (visceral hypersensitivity) and central nervous system dysregulation of the modulation of gut signaling and motor function (Drossman, 2016). They represent the most common diagnoses in gastroenterological units, their natural course tends to be chronic with alternate phases of remission and exacerbation, their prognosis is good because of the lack of anatomic involvement and therefore their major clinical consequence consists in reducing, more or less, the quality of life of patients.

It is evident that the complexity of their pathophysiological alterations, including motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous processing, cannot benefit from a single pharmacological agent with an exclusive effect on a specific target. Instead, therapeutic substances with non-pharmacological properties, but able to act by affecting or modulating different pathogenetic features, even though with unknown mechanisms of action, like MDMS, might have a role in alleviating symptoms of patients with functional gastrointestinal disorders. This potential effect has been already substantiated by many clinical trials performed with the clinical trial standards adopted for traditional medicinal products and therefore both their efficacy and safety have been objectively evaluated in the interest of patients undergoing this kind of treatment.

3.1 Esophageal disorders

Functional esophageal disorders present with typical symptoms (mainly heartburn and regurgitation) that are not associated with structural, inflammatory or major motor abnormalities. Thus, these patients have a normal endoscopy and no evidence of both eosinophilic esophagitis or achalasia and esophageal spasm or abnormal esophageal acid exposure. According to Rome IV criteria (Aziz et al., 2016), they are mainly represented by functional chest pain, reflux hypersensitivity and functional heartburn. The majority of these patients do not respond to PPI therapy because the pathogenetic role of acid is absent or very poor in them (Savarino et al., 2013a).

The pathophysiology of these disorders is complex and still unclear, but different factors seem to be implicated. It has been hypothesized that there is a combination of peripheral and central factors that interplay to increase esophageal perception. An increased permeability of esophageal mucosa due to an altered integrity with dilation of intercellular spaces (Savarino et al., 2013b) may allow noxious sensitizing luminal substances access to deeper layers of the esophagus, where they may induce an inflammatory response; then signals are transferred *via* spinal cord to the brain and an abnormal central processing may contribute to generate symptoms, in particular heartburn. Psychological factors, such as anxiety, may enhance the perception of peripheral stimuli of chemoreceptors and mechanoreceptors.

Given that abnormal peripheral sensitization and central processing are considered relevant in the pathogenesis of

TABLE 1 Randomized and controlled studies with MDMS in esophageal functional disorders.

Authors, year	Types of disorder	No. of cases	Types of intervention	Results
Palmieri et al. (2013)	NERD	20	HA + CS vs. placebo x 2 weeks	Significantly higher relief of symptoms with MDMS ($p < 0.01$)
Savarino et al. (2017)	NERD	154	HA + CS + PPI vs. PPI + placebo x 2 weeks	Significant improvement of reflux symptoms with MDMS + PPI ($p < 0.01$)
Ribaldone et al. (2021)	NERD	20	HA + aminoacid mixture and rice extract vs. placebo x 2 weeks	Significantly higher relief of reflux symptoms with MDMS ($p < 0.0001$)
Pellegatta et al. (2022)	GERD with extraesophageal symptoms	71	HA + CS + aloe and honey combined with PPI vs. PPI alone x 6 weeks	No statistical difference between the two treatments on the relief of atypical symptoms ($p > 0.05$)

Abbreviations: NERD, non-erosive reflux disease; HA, hyaluronic acid; CS, chondroitin sulphate; MDMS, medical device made of subctances; PPI, proton pump inhibitors; GERD, gastroesophageal reflux disease.

esophageal functional disorders, the treatment remains empiric and the use of pain modulators is strongly suggested (Fass et al., 2021). However, clinical trials aimed at assessing the efficacy of these drugs are scarce and disappointing (Savarino et al., 2020). On the contrary, there is some evidence that MDMS may be helpful in these conditions.

3.2 Examples of randomized and controlled studies with MDMS

Table 1 reports the most important features of the placebo-controlled clinical trials we have evaluated in the field of esophageal functional disorders.

Among the MDMS available for the treatment of functional esophageal disorders, one of the most important and most studied is represented by the combination of hyaluronic acid (HA), which is well known for its regeneration properties and tissue repair, and chondroitin sulphate (CS), which has an anti-inflammatory and mucosal protective activity (Savarino et al., 2017). These two substances are linked to poloxamer 407, which provides high adhesive properties and permits to prolong the contact time with esophageal mucosa. This compound acts as a physical barrier and not as a chemical agent.

(Di Simone et al., 2012) performed an experimental study on the esophageal mucosa of pigs and, using Evans blue as a dye which appears when there is an increased mucosal permeability, they showed that there is no stain when the above compound was added to an acid damaging solution given for 90 min, thus confirming its very high esophageal protective effect.

From a clinical point of view, (Palmieri et al., 2013) studied a small group of 20 patients with typical symptoms of non-erosive reflux disease (NERD), that is heartburn and regurgitation. They received four daily doses of HA + CS for 2 weeks and placebo with a cross-over design. The authors found that this combination relieved symptoms significantly more than placebo ($p < 0.01$).

Later, our group (Savarino et al., 2017) performed a larger study enrolling 154 patients with NERD. They were subdivided into two groups receiving HA + CS and PPIs or PPIs + placebo. One dose of PPIs and four daily doses of HA + CS and placebo were given each day for 2 weeks. HA + CS added to PPIs was able to reach the primary end point, that is the reduction of the total symptom score by at least three points, in 52% of patients compared with 32% of PPIs + placebo and this difference was highly significant ($p < 0,01$). Also the quality of life evaluated with the SF-36 questionnaire resulted to be improved with the former combination, in particular general health and social functioning. Therefore, HA + CS are able to ameliorate both reflux symptoms and quality of life in NERD patients, when given both alone or associated with PPIs in comparative studies with placebo. The adverse events recorder during the study resulted to be similar in patients treated with MDMS and placebo.

Another small study by (Ribaldone et al., 2021) assessed the efficacy and safety of a patented oral formulation (liquid sachets containing HA + *a* mixture of amino-acids including proline, hydroxy-proline and glutamine, and rice extract dispersed in bio-adhesive polymer matrix) in a randomized, double-blind and placebo-controlled study enrolling 20 NERD patients with heartburn, who were treated with three sachets per day for 2 weeks. The authors found that a three-point reduction in the total symptom score was achieved in 95% of patients with the investigational product against 20% of patients with placebo ($p < 0,0001$). No adverse events were reported.

Finally, (Pellegatta et al., 2022) evaluated the efficacy of a 6-week treatment with a MDMS consisting of HA + CS and aloe + honey combined with PPI against PPI monotherapy in 71 patients with extra-esophageal symptoms of GERD. The comparison between groups did not show statistically significant differences, while the combined product was significantly superior to PPI alone for individual items of the total Reflux Symptom Index (RSI). This is the first published study on the effects of a new MDMS in the treatment of a difficult condition, such as GERD presenting with extra-esophageal symptoms. Only minor adverse events have been documented in this clinical study.

4 Functional dyspepsia

At least 20% of the general population has chronic recurrent symptoms that can be attributed to disorders of gastroduodenal function and these people do not have any evidence of organic causes (Tack et al., 2006). Functional dyspepsia (FD) is characterized

TABLE 2 Randomized and controlled studies with MDMS in patients with functional dyspepsia.

Authors, year	Type of disorder	No. of cases	Types of intervention	Results
Chey et al. (2019)	Functional dyspepsia	95	Caraway oil + L menthol vs. placebo for 2 weeks	Significantly higher reduction of symptoms with MDMS ($p < 0.039$)
Rich et al. (2017)	Functional dyspepsia	114	Peppermint + caraway oil vs. placebo x 4 weeks	Significantly higher relief of symptoms with MDMS ($p < 0.001$)

Abbreviation: MDMS, medical device made of substances.

by one or more of the following symptoms: Post-prandial fullness, early satiation, epigastric pain and epigastric burning. Two groups of patients have been identified: Patients with post-prandial distress syndrome (PDS), which is characterized by meal-induced dyspeptic symptoms and epigastric pain syndrome (EPS), which refers to symptoms that do not occur exclusively post-prandially, but can also occur during fasting. In an additional group, the two syndromes can overlap (Stanghellini et al., 2016).

The pathophysiology of FD is complex and multifactorial, like the one showed for esophageal functional disorders. It is far from being elucidated and comprises gastroduodenal motor and sensory dysfunction, as well as impaired mucosal integrity, low-grade immune activation and dysregulation of the gut-brain axis. Acid hypersecretion is not implicated in the pathogenesis of FD (Savarino et al., 2011) and also H. pylori infection has a modest role (Blum et al., 1998). The association of dyspepsia and psychiatric disorders, such as anxiety, depression and neuroticism, is commonly recognized (Henningsen et al., 2003).

Treatment is empiric and generally addressed to control at least one of the pathophysiological factors sustaining the most disturbing symptoms. Although many clinical trials using the traditional pharmacological agents (PPIs, prokinetics, anti-Helicobacter antibiotic regimens, pain modulators, etc.,) have been made, the results have been frequently partial and unsatisfactory (Talley, 1991). Even the adoption of psychological therapies has not provided convincing benefit because of the small sample sizes and poorly matched treatment groups (Stanghellini et al., 2016).

4.1 Examples of randomized and controlled studies with MDMS

Overall, it is not surprising that no single pharmacological agent was shown to control adequately the complex pathophysiological alterations of FD and therefore these patients continue to suffer from their symptoms even for the entire life, whose quality is greatly reduced. However, several randomized and controlled clinical trials using MDMS have been published in recent years and showed promising results. They are displayed in Table 2.

(Chey et al., 2019) conducted a randomized and controlled trial, which evaluated a novel formulation of caraway oil and L-menthol *versus* placebo in patients with FD defined by Rome III criteria (Tack et al., 2006). Ninety-five patients were randomized to receive the investigational product (two capsules per dose, twice per day) or placebo and efficacy was measured at 24 h, 2 weeks, and 4 weeks. At 24 h, the active arm reported a statistically significant reduction in PDS symptoms ($p < 0.039$). In patients with more severe symptoms, approximately 3/quarter of them showed substantial global improvement for those with EPS syndrome ($p < 0.046$) after 4 weeks of treatment against half in the control arm. Overall, this study showed that the combination of caraway oil and L-menthol was able to provide rapid resolution of symptoms (within 24 h) and to control severe FD with EPS symptoms after 4 weeks of treatment compared with placebo.

In an additional study (Rich et al., 2017) assessed the efficacy of a fixed peppermint/caraway oil combination (Menthacarin) on symptoms and quality of life of patients with FD (both PDS and EPS), performing a prospective, double-blind trial with 114 outpatients who were randomized to receive this compound or placebo (2 × 1 capsule/day) for 4 weeks. After 2 and 4 weeks, active treatment was superior to placebo in alleviating symptoms in both forms of dyspepsia ($p < 0.001$). The authors concluded that Menthacarin is an effective therapy for the relief of pain and discomfort and the improvement of the quality of life in patients with FD, suffering from both EPS and PDS forms.

5 Functional bowel disorders

They are a spectrum of chronic gastrointestinal disorders characterized by predominant symptoms of abdominal pain, bloating, distension and/or bowel habits abnormalities (constipation, diarrhea, or mixed constipation and diarrhea). These disorders are not due to anatomic abnormalities identified by routine diagnostic examinations. The main categories are the following: Irritable bowel syndrome (IBS), functional constipation (FC), and functional diarrhea (FDr) (Longstreth et al., 2006).

5.1 Irritable bowel syndrome

IBS is characterized by recurrent abdominal pain combined with change in bowel habits (constipation, diarrhea or mixed constipation and diarrhea). There are frequently associated symptoms of abdominal bloating/distension. The pathophysiology is complex and multifactorial and includes altered gastrointestinal motility, visceral hypersensitivity, increased intestinal permeability, prior enteric infections, immune activation, altered microbiota, and disturbancies in brain-gut interaction (Mearin et al., 2016). Moreover, the presence of psychological alterations is frequent in IBS patients and may interplay with the above multiple factors. Treatment is based on the control of the mostly disturbing symptoms and therefore many pharmacological agents are

TABLE 3 Randomized and controlled studies with MDMS in patients with functional bowel disorders.

Authors, year	Types of disorder	No. of cases	Types of intervention	Results
Strisciuglio et al. (2021)	Functional constipation in children	158	Complex of honeys + aloe and Mallow polysaccharides (Promelaxin) microenemas vs. polyethylene glycol (PEG) 4,000 × 2 weeks	Non-inferiority of Promelaxin microenemas compared with PEG 4000 in alleviating constipation
Minguez et al., 2016	Functional constipation in adults	1,099	Systematic review of 12 studies comparing PEG vs. placebo	Significant increase in stool number with PEG
Lee-Robichaud et al. (2010)	Functional constipation in adults and children	868	Meta-analysis of 10 studies (RCTs) comparing PEG vs. lactulose	PEG was better than lactulose in outcomes of stool frequency, form of stools and relief of abdominal pain
Gordon et al. (2016)	Functional constipation in children	101 (PEG vs. placebo)	Meta-analysis of 2 RCTs in children FC comparing PEG vs. placebo, 6 RCTs comparing PEG vs. lactulose and 3 RCTs comparing PEG vs. milk of magnesia	Significantly increased number of stools per week with PEG compared with placebo, lactulose and milk of magnesia, respectively
		465 (PEG vs. lactulose)		
		211 (PEG vs. milk of magnesia)		

Abbreviations: MDMS, medical device made of substances; PEG, polyethylene glycol; RCT, randomized controlled trial; FC, functional constipation.

usually adopted, but the benefit is limited and the natural history of the disease does not change.

5.2 Functional constipation

This is a disorder in which symptoms of difficult, infrequent or incomplete defecation predominate, while abdominal pain is absent or minimal. Similar to IBS, it is due to a variety of pathophysiological processes and moreover psychological factors may be frequently associated. Medical therapy is empiric and based on different options that do not modify the course of the disorder which remains chronic and recurrent.

5.3 Functional diarrhea

This form is characterized by recurrent passage of loose or watery stools and this is the predominant symptom, while abdominal pain is generally lacking or poorly represented. Once again, there is no single pathophysiological alteration capable to explain the cause of symptoms and, like IBS, various mechanisms contribute to generate the clinical manifestations of the disorder, including both physiologic and psychosocial factors. Treatment is addressed to control the main symptom diarrhea with several pharmacological products, which however are not able to cure definitely the disease.

5.4 Examples of randomized and controlled studies with MDMS

As above-mentioned, patients with functional bowel disorders are treated with a wide variety of drugs and forms of psychotherapy, but the multiplicity of therapy proves that none is strikingly effective, an observation made daily by clinicians caring for these patients (Klein, 1988). Many factors are implicated in symptom generation and therefore a single agent does not provide notable enduring success. For these reasons the use of MDMS may be helpful in reaching good therapeutic results and many clinical trials have already shown that they are effective and safe in many patients. Particularly those with FC, both children and adults, have been the object of multiple studies and various meta-analyses, as shown in Table 3.

(Strisciuglio et al., 2021) conducted a randomized non-inferiority trial in order to assess whether microenemas of Promelaxin (A complex of honeys + Aloe and Mallow polysaccharides) are not inferior to oral polyethylene glycol (PEG) 4,000 as topical therapy in children with FC according to Rome III criteria (Longstreth et al., 2006). They enrolled infants and young children aged 6–48 months who were randomized to 2 weeks of Promelaxin microenemas or PEG daily, followed by a 6-week on-demand treatment period. The primary endpoint was defined as to achieve at least three evacuations per week and an average increase of at least one evacuation per week as compared to baseline. One hundred and fifty-eight patients were recruited and the study showed that Promelaxin in microenemas was not inferior to PEG 4,000 in reaching the primary objective (response rate difference: 16,5%, CI 1.55%–31,49%, with Promelaxin *versus* 11,03%, CI 5.58%–27,64%) with PEG.

A recent review (Mínguez et al., 2016) has evaluated the evidence published on the use of PEG, with or without electrolytes, against placebo in the management of FC and found that all studies showed a significant superiority regarding stool number, less straining, less need for rescue laxatives and lower dropout number in patients taking PEG. Remarkable secondary effects were not observed.

In a Cochrane review from 2010, (Lee-Robichaud et al., 2010) performed a meta-analysis of clinical trials published between 1997 and 2007 that comparatively evaluated PEG solutions with lactulose for FC treatment. They included ten trials in the review with a total of 868 patients and concluded that PEG is superior to lactulose regarding the increment in the number of stool passages/week, form of the stool, decrease in bowel pain and reduction in the use of associated laxatives.

Finally, (Gordon et al., 2016) assessed the efficacy and safety of osmotic laxatives used to treat FC in children and concluded that PEG preparations were superior to placebo, lactulose and milk of magnesia in terms of increased number of stools per week. The adverse events included flatulence, abdominal pain, nausea, diarrhea and headache.

6 Discussion and conclusion

In the last decades we have witnessed revolutionary improvements in the science and therapy of several gastroenterological diseases that have been controlled adequately or cured definitively. They are represented by the so-called acid-related diseases, in particular GERD, and by two relevant infectious illnesses, such as peptic ulcer and chronic hepatitis C, which have been resolved with the use of antimicrobial or antiviral agents acting on single pharmacological targets able to block the replication of both *H. pylori* or HCV.

However, pharmacological agents have remarkable limitations when adopted to cure patients with other digestive disorders, which are characterized by multifactorial and not fully elucidated pathophysiological alterations that are difficult to treat with traditional drugs whose effect is based on a specific and precise mechanism of action. These disorders affect the entire gastroenteric tract, are very frequent and present a chronic and recurrent natural history. Due to their complex pathogenesis and the absence of anatomical abnormalities, they are named functional disorders because of the supposed dysfunction of the brain-gut interaction in the generation of their symptoms.

These patients with gastrointestinal functional disorders are the most suitable candidate for the use of MDMS in the field of gastroenterology. Indeed, the pathophysiological mechanisms inducing these widespread clinical conditions are complex and poorly understood and therefore they do not benefit from pharmacological agents acting on a single target. The use of MDMS, whose mechanism of action is not pharmacological, but may be linked to a multiple synergistic effect on many different factors, can control better the symptoms of these patients. A medical device made of complex or natural substances and devoid of a single target effect can profitably and synergistically act on the multiple factors implicated in the pathogenesis of these diseases. The non-pharmacological effect of MDMS is favored by the fact that the digestive tract has the fundamental function of being a barrier that can be reinforced physically by the use of agents with non-specific mechanism of action.

There are already many clinical trials, performed with the well-known standards of randomized and controlled studies, that seem to confirm their efficacy and safety in the treatment of the various functional illnesses pertaining to the gastroenterological world. So far, the controlled clinical studies performed and evaluated in our paper have confirmed that MDMS are safe and the adverse events registered in the various RCTs are of minor severity and superimposable to those of placebo. Obviously, the post-marketing surveillance plays a central role in collecting and managing any report on adverse events and reactions regarding these products.

Author contributions

VS review concept, data analysis, drafting and finalizing of manuscript EM search and collection of literature PZ search and collection of literature, critical review of manuscript MF search and collection of literature, drawing of figures GB search and collection of literature EG critical review of manuscript EV critical review of manuscript, drafting and finalizing of manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Safety and efficacy of substance-based medical devices: Design of an *in vitro* barrier effect test

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This study aims to develop an *in vitro* barrier effect test over biomimetic membrane, which is useful to establish the film forming ability of a substance-based medical device (SB-MD). The method contemplates a multiparametric approach including: *i*) the measurement of the transmembrane passage of a molecular-like marker over a lipid-impregnated biomimetic membrane (simulating the skin and gastro-intestinal and buccal tissues) by using a static diffusion cell apparatus (Franz cell); and *ii*) the evaluation of the integrity of the membrane (colorimetric test). In the first step, a series of lipid-impregnated biomimetic membranes (simulating gastro-intestinal, buccal, and skin tissues) were implemented and their permeability performance validated using model drugs (caffeine and acyclovir) by referring to literature data. As a result, the apparent permeability (P_{app}) of caffeine over the biomimetic gastro-intestinal membrane (P_{app} = 30.5E-6 cm/s) was roughly comparable to the literature values obtained with Caco-2 cell line membrane (P_{app} = 30.8E-6 cm/s) and with the Franz cell method (P_{app} = 36.2E-6 cm/s). Acyclovir was shown to be a poorly permeable substance both in the literature and experimental data. Following this step, the permeability study was extended to both biomimetic buccal and skin (STRAT-M®) membranes: for caffeine, biomimetic gastro-intestinal membrane was the most permeable (P_{app} = 30.5E-6 cm/s), followed by the buccal (P_{app} = 18.2E-6 cm/s) then the skin (P_{app} = 0.5E-6 cm/s) biomimetic membranes. In a second part of the work, the barrier effect test was developed following a similar permeability-like approach. The protocol was designed with the idea of assessing the capacity of a certain product to prevent the passage of caffeine across the biomimetic membrane with respect to a negative and positive control. The untreated membrane was the negative control, while membrane covered with a Vaseline film was the positive. As a last step, the developed barrier effect protocol was applied to an experimental gel-like SB-MD under development for the treatment of aphthae (Aphthae gel, an invented trade name), herein used as a case study. Regarding the results, Aphthae gel reduced the caffeine passage by 60.3%, thus highlighting its effectiveness to form a protective film. Overall, these results provide important knowledge and may pave the way for the use—including for industrial applications—of these simple but effective biomimetic membranes for carrying out high throughput screening necessary to design safe and effective SB-MDs before proceeding further with clinical trials, as requested by the regulations.

KEYWORDS

medical devices, franz cell, biomimetic membrane, permeability, barrier effect, nutraceuticals

1 Introduction

In response to the new European Regulations for substance-based medical devices (SB-MD), there is the necessity to deeply study their safety and efficacy and thus to develop new experimental protocols to demonstrate the concept of their non-pharmacological mechanisms of action (UE, 2021; Giovagnoni, 2022). By definition, "*substance-based medical devices are medical devices that are composed of substances or combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body*". Although they are herbal-like medicinal products in their presentation and pharmaceutical form, they achieve their principal intended effect *via* a physicochemical and/or physical mechanism of action (including mechanical action, a physical barrier such as a film, lubrication, hydration or dehydration, and pH modification) (Fimognari et al., 2022; Manellari et al., 2022). The ISO 10993 sets a series of standards and guidance for the biological evaluation of medical devices within a risk management process as part of the overall evaluation and development of the medical device (ISO, 2020). In this context, the ISO 10993-2 describes animal welfare aspects regarding the performing of animal studies for the biological evaluation of medical devices, thereby also emphasizing the 3Rs: the replacement, reduction, and refinement of animal studies. ISO 10993-1,-2, and −23 promote the use of *in vitro* tests instead of *in vivo* to support animal welfare, saying that "*in vitro tests have preference over in vivo tests when appropriately validated and providing equally relevant information to that obtained from in vivo tests*". Despite these standards, to date there is no regulatory reference explaining in detail the operational procedures needed to evaluate the safety and effectiveness of SB-MDs.

Therefore, in this study, the barrier effect method was developed using an *in vitro* animal-free biomimetic approach to evaluate the film-forming ability of SB-MDs as a part of the experimental process necessary to establish the safety and effectiveness of SB-MD products. The barrier effect is necessary to measure the ability of a given device to protect human tissues from external agents by promoting the maintenance of its normal physical-chemical balance. From a technical point of view, the herein proposed barrier effect assay takes advantage of the permeability study test, in which caffeine was selected as a probe to assess the propensity of a given product to form a protective film due to its ability to permeate different models of human tissue even in the absence of damage. Moreover, caffeine is the chemical reference for *in vitro* absorption studies as stated by the OECD 428 and related Guidance Documents (OECD, 2004). In general, a permeability assay measures the flux and the kinetic profile of a defined substance from a donor into an acceptor compartment through the respective membrane (di Cagno et al., 2015). The kinetic profile reflects the changes in drug concentration over time and diffusion through the membrane. The permeability coefficient calculated out of this study determines the rate of migration of a substance through the membrane. For this purpose, several well-characterized *in vitro* permeability prediction methods have been developed in recent decades (Corti et al., 2006a; Corti et al., 2006b). Moreover, many organizations [i.e., the Organization for Economic Co-operation and Development (OECD), the United States Environmental Protection Agency, and the European Commission Scientific Committee on Consumer Products (SCCP)] have produced extensive guidelines to assist companies and organizations towards the implementation of harmonized *in vivo* and/or *in vitro* absorption studies (OECD, 2004; SCCP, 2010; Hopf et al., 2020). Regarding absorption, the above-described guidelines for the *in vitro* methodologies outline the following criteria: *i*) the use of static diffusion cell apparatus; *ii*) the use of an appropriate membrane positioned between the upper and lower chambers of a static diffusion cell; *iii*) the test sample should remain in contact with the membrane on the donor side for a defined period (from 0.5 h up to 24 h); *iv*) the receptor fluid may be a degassed saline or buffered saline solutions having a physiological pH and temperature; *v*) the receptor fluid should be sampled to obtain an absorption-time profile by quantifying a defined marker compound *via*, for example, high-performance liquid chromatography (HPLC) and/or UV-Vis spectroscopies; and *vi*) at the end of the experiment, the integrity of the membrane should be checked by evaluating the penetration of a marker molecule. In general, however, these indications are intended to be modulable and any deviation from this principle is possible when justified by the study case.

Accordingly with those publications and guidelines, herein, the Franz cells system was used as a static diffusion cell. This apparatus has been widely used to study the *in vitro* permeation of pharmaceutical, nutraceutical, or topical products thanks to its simplicity, reproducibility, and cost-effectiveness (Ng et al., 2010; Casiraghi et al., 2017; Salamanca et al., 2018). Moreover, the system was previously validated by Texeira et al., who studied the intestinal permeability of BCS model drugs over biomimetic intestinal membranes, comparing the data with Caco-2 cells (Teixeira et al., 2020).

Focusing on the membrane, many different human (e.g., human cadaver, surgical biopsies, and skin from cosmetic surgeries) or animal (e.g., pig, rodent) tissues can be in principle used to carry out a permeability test. However, the use of biological tissue has several drawbacks, including ethical issues, difficult and time-consuming preparation, handling, and maintenance of freshly excised tissues, the possibility of tissue damages, and high sample to sample biological variability even within the same species (e.g., depending on age, sex, race), with consequently poor reproducibility in permeation results and lack of full resemblance with *in vivo* data. For these reasons, in recent years, artificial biomimetic membranes have progressively gained interest as an alternative model to *in vivo* applications. Moreover, several studies have been published demonstrating a good relationship between the permeability data for transcellularly transported drugs measured using synthetic membranes and those obtained with cell-based model tissue (Corti et al., 2006a; Corti et al., 2006b; Haq et al., 2018a; Berben et al., 2018; Haq et al., 2018b; Mura et al., 2018; Teixeira et al., 2020; Fedi et al., 2021). It is worth noting this biomimetic membrane may be correctly predicting only the passive transcellular absorption because these artificial membranes do not have any transporters. However, since most commercial drugs (80%–95%) are primarily absorbed by passive diffusion (Loftsson et al., 2006; Di et al., 2012), the use of artificial membranes offers an effective high throughput approach for the drug absorption and represents a very useful tool for the early stages of pre-clinical studies. Moreover, synthetic membranes are also

preferred as they are more easily resourced, less expensive, and structurally simpler than real tissue. Furthermore, they exhibit superior permeation data reproducibility as *in vivo* variables are eliminated.

From a structural point of view, the artificial biomimetic membrane is a multi-component system formed by a porous polymeric support with a very tightly packed lipidic-like surface layer that creates a defined organization at the molecular level resembling both the morphology and the lipophilic properties observed in the desired human biological barrier. Generally, the superficial lipidic film is composed of an oleic mixture of phospholipids and sterols (Corti et al., 2006a; Corti et al., 2006b; Eeman and Deleu, 2010; Khdair et al., 2013; Mura et al., 2018). As recently separately reported by Corti et al., Mura et al., and Khdair et al., biomimetic artificial membranes may be efficiently produced starting from different dialysis membranes opportunely impregnated with a mixture of n-octanol, Lipoid®E80, and cholesterol (Corti et al., 2006a; Corti et al., 2006b; Khdair et al., 2013; Mura et al., 2018). In their publications, the authors systematically tested a series of polymeric filters with different structural and chemical natures (e.g., type of polymer, pore size, percent of porosity, and thickness) impregnated with a diverse ratio of the lipidic mixtures. The purpose of these studies was to reproduce these artificial membranes and use them to predict drug absorption in human gastro-intestinal and buccal tissues.

In addition to intestinal and oral absorption, dermal absorption assays are used to predict risks from the exposure to chemicals as well as to demonstrate the efficacy of cosmetics, medical devices, and of some topical-delivery therapeutic active ingredients. In the past, the most used dermal tissue was "*ex-vivo*" porcine skin, despite its lower barrier function compared with human skin. Nowadays, also for ethical reasons, the use of animal tissues has been restricted and, thus, numerous skin surrogate systems and human skin equivalents (HSEs) have been developed (Pellegatta et al., 2020). In this context, Strat-M® is the most used synthetic non-animal-based membrane model for transdermal diffusion tests. This membrane is a multi-layered polyether sulphone support specially designed to mimic the skin structure (e.g., stratum corneum, dermis, and subcutaneous tissue) and covered with skin lipids (e.g., ceramides, cholesterol, and free fatty acids). The hydrophobic lipidic mixture coated on the membrane is composed of the main stratum corneum lipids. The polyether sulfone cut-off has been designed to mimic the human skin morphology more closely than other artificial membranes. These physio-chemical properties make the Strat-M® membrane an interesting and recommended model alternative to evaluate the skin permeability of molecules. Moreover, many studies have shown that Strat-M® membrane can be used as a surrogate for human skin to study the diffusion characteristics of a wide range of compounds for topical and transdermal formulations, providing close transport correlation characteristics to human skin (Haq et al., 2018a; Haq et al., 2018b).

With this work, we demonstrate that it may be possible to exploit the use of these simple and effective biomimetic membranes for developing a barrier effect test. The results of this study show that biomimetic membranes represent a useful tool for the preliminary high throughput screening of film forming formulation candidates to be further tested for their efficacy and safety in clinical trials, as requested by the regulations related to SB-MDs.

The protocols here proposed were adequately designed to be suitable for industrial use, for which having an experimental high throughput screening is fundamental to quickly creating safe and effective formulations. As a case study, the method was then applied to an experimental gel-like SB-MD under development for the treatment of aphthae (Aphthae gel, an invented trade name). This SB-MD was designed for the treatment of aphthae, stomatitis, and microlesions of the mouth. It forms a protective film on microlesions that, thanks to the effectiveness of selected natural extracts, reduces painful symptoms and burns and promotes re-epithelialization phenomena.

2 Materials and methods

2.1 Materials

Polymeric dialysis-like supports were purchased from Millipore® (Mixed Cellulose Esters VCWP02500, 0.1 µm × 25 mm, white plain; Mixed Cellulose Esters VSWP02500, 0.025 µm × 25 mm, white plain; New York, NY, United States). The lipid phase used for the impregnation of the porous supports consisted of Lipoid® E80 by Lipoid (Ludwigshafen, Germany), and cholesterol and *n*-octanol purchased from Sigma–Aldrich (Milan, Italy). Caffeine and acyclovir reference standards were purchased from Merck (Darmstadt, Germany). Water (HPLC grade), methanol (HPLC grade) and acetonitrile (HPLC grade) were purchased from Carlo Erba Reagents (Cornaredo, Milan, Italy). All reagents were used without further purification. Aphthae gel was provided from Labomar (batch K1861 T, exp 2024/07).

2.1.1 Instrument and chromatographic conditions

The standard stock solutions quantification was performed using a UV-1280 spectrophotometer (Shimadzu, Japan). The HPLC-UV analyses were performed on VANQUISH Core/Ultimate 3,000 from Thermo Fisher Scientific (Waltham, Massachusetts, United States) which included a pump, autosampler, column oven, and diode array detector (DAD). The reverse phase column Acclaim™ C18 (150 mm × 4.6 mm, 5 mm particle size) from Thermo Fisher Scientific (Waltham, United States) was used and maintained at 20°C. The injection volume of standards and samples were 10 µL for caffeine standard solutions and 20 µL for acyclovir standard solutions. The detector wavelength was set at 275 nm for caffeine and 254 nm for acyclovir. The mobile phase for the methods consisted of A: water, B: acetonitrile and C: methanol. The analytical methods for caffeine and acyclovir were validated using the elution gradients reported in Supplementary Tables S13, S14. The data were acquired with a Chromeleon 7 (Thermo Fisher Scientific, Waltham, Massachusetts, United States) and processed using Microsoft Excel (Microsoft, Redmond, Washington, United States).

2.2 Methods

2.2.1 Sample preparation for HPLC analysis

2.2.1.1 Stock and standard solutions

Stock solutions were prepared by weighing 50 mg of caffeine reference standard and 25 mg of acyclovir reference standard into

50 mL (MeOH 20% *v/v* in water) and 20 mL (ACN 2% *v/v* in water) volumetric flasks, respectively. The standard solutions were stirred for 1 h and the concentrations were checked *via* UV-vis spectrophotometry analysis. For the caffeine stock solution, 963 μg/mL was derived and 1,180 μg/mL was derived for the acyclovir stock solution. The caffeine standard solutions were prepared by diluting a specific amount of stock solution in the solvent (MeOH 20% *v/v* in water) to obtain a range of concentrations: 0.94 μg/mL, 4.7 μg/mL, 9.6 μg/mL, 24.0 μg/mL, 48.2 μg/mL, 77.0 μg/mL, 93.5 μg/mL, 115.6 μg/mL, and 192.6 μg/mL. Moreover, for LOD and LOQ determination, concentrations of 0.03 μg/mL and 0.05 μg/mL were prepared, respectively. Acyclovir standard solutions were prepared by diluting a specific amount of stock solution in the solvent (ACN 2% *v/v* in water) to obtain a range of concentrations: 0.1 μg/mL, 0.5 μg/mL, 1 μg/mL, 5 μg/mL, 10 μg/mL, 25 μg/mL, and 50 μg/mL. For acyclovir LOD and LOQ determination, concentrations of 0.03 μg/mL and 0.05 μg/mL were prepared, respectively. Each standard solution was filtered through a 0.20 μm syringe filter.

2.2.1.2 Specificity

The samples for specificity evaluation consisted of: placebo solutions (PBS buffer solutions without caffeine or acyclovir) and PBS solutions spiked with 100% of analyte. PBS buffer was prepared as follows: NaCl 8.00 g/L, KCl 0.200 g/L, $Na_2HPO_4{\cdot}2H_2O$ 1.44 g/L, and KH_2PO_4 0.245 g/L were dissolved in water and pH was adjusted to 7.4. The placebo sample for caffeine was prepared by diluting PBS buffer in MeOH 20% *v/v* in water (1:10), and the placebo sample for acyclovir was prepared by diluting PBS buffer in ACN 2% *v/v* in water (1:10). Spiked sample solutions were prepared by weighing 10 mg of caffeine reference standard and 1 mg of acyclovir reference standard into 10 mL volumetric flasks and solubilized in PBS buffer. Dilutions of 1:10 were used in MeOH 20% *v/v* in water for caffeine and ACN 2% *v/v* in water for acyclovir. For the Aphthae gel case study, the samples consisted of: placebo solutions with 200 mg of Aphthae gel in PBS buffer (without caffeine or acyclovir) and spike solutions with 200 mg of Aphthae gel in PBS buffer with spike 100% analyte addition (with caffeine or acyclovir). Caffeine and acyclovir placebo samples were prepared by weighing 200 mg of Aphthae gel and dissolving in 10 mL volumetric flasks containing PBS buffer. The solution was stirred for 1 h at room temperature. Before injection, a 1:10 dilution in MeOH 20% *v/v* in water was used for caffeine, and the placebo sample for acyclovir was prepared by diluting Aphthae gel PBS buffer solution in ACN 2% *v/v* in water (1:10). Additionally, spiked sample solutions were prepared by weighing 10 mg of caffeine reference standard and 1 mg of acyclovir reference standard into two different 10 mL volumetric flasks with 200 mg of Aphthae gel and solubilized in PBS buffer. The solutions were stirred for 1 h at room temperature. Dilutions of 1:10 were used in MeOH 20% *v/v* in water for Caffeine and ACN 2% *v/v* in water for acyclovir. Each sample was filtered through a 0.20 μm syringe filter and single injection was performed.

2.2.1.3 Precision and accuracy

Caffeine spiked sample solutions were prepared by weighing 8, 10, and 12 mg of caffeine reference standard into 10 mL volumetric flasks and solubilized in PBS buffer. The same was done for acyclovir spiked sample solutions, by weighing 0.8, 1, and 1.2 mg of acyclovir reference standard. Dilutions of 1:10 were used in MeOH 20% *v/v* in water for caffeine and ACN 2% *v/v* in water for acyclovir. For the Aphthae gel case study, caffeine spiked sample solutions were prepared by weighing 8, 10, and 12 mg of caffeine reference standard into 10 mL volumetric flasks with 200 mg of Aphthae gel and solubilized in PBS buffer. The solutions were stirred for 1 h at room temperature. The same was done for acyclovir spiked sample solutions, by weighing 0.8, 1, and 1.2 mg of acyclovir reference standard. Dilutions of 1:10 were used in MeOH 20% *v/v* in water for caffeine and ACN 2% *v/v* in water for acyclovir. Each sample was filtered through a 0.20 μm syringe filter and triplicate injection was performed.

2.2.2 Preparation of biomimetic membrane

The membrane's support was functionalized by immersion in a lipid mixture solution composed of phospholipids (Lipoid® E80), cholesterol, and n-octanol for 60 min at room temperature. Briefly, the lipid phase solution for the preparation of intestinal membranes was a mixture of 1.7% phospholipids (Lipoid® E80, Ludwigshafen, Germany), 2.1% cholesterol (Sigma–Aldrich Chemical Co., Milan, Italy), and 96.2% *n*-octanol (Sigma–Aldrich Chemical Co., Milan, Italy); for the preparation of buccal biomimetic membrane, the lipid phase solution was composed of 3.3% Lipoid E80, 3.2% cholesterol, and 93.5% *n*-octanol. Excess lipids were absorbed with filter paper over 30 min. Next, all impregnated membranes were weighed, evaluated to check for accuracy (intestinal membranes: 50% ± 5; buccal 41% ± 2), and then stored in a freezer for at least 24 h for stabilization.

2.2.3 Permeability studies

Permeability studies were performed with a Franz cell (Copley Scientific, United Kingdom), studying the permeability of specific compounds through the membrane. Impregnated artificial membranes were positioned between upper and lower part of the diffusion cells. The receiving chamber (10.5 mL) was filled with degassed phosphate-buffered solution (PBS), pH 7.4 (USP 32), left under stirring (200 rpm) and the temperature was kept constant (37.0°C ± 0.5°C). In the donor, 1 mL of drug (caffeine 10 mg/mL, acyclovir 1 mg/mL) was added and covered to prevent evaporation. Samples from the receiving chamber were collected from 0 up to: 4 h for intestinal membranes, 3 h for buccal membranes, and 24 h for STRAT-M®, and then analysed by HPLC (Vanquish, Thermo-scientific, United States). The sampling volume was immediately replaced with the same volume of fresh PBS prewarmed solution at 37°C ± 0.5°C.

At the end, the concentration in the receiving chamber, the flux (g/s·cm^2), and apparent permeability (cm/s) were determined using Equations 1, 2, as described in ref. 15.

$$\mathbf{J} = \frac{\mathbf{dQ}}{\mathbf{dt}}\mathbf{A} \tag{1}$$

$$\mathbf{P_{app}} = \frac{\mathbf{J}}{\mathbf{C_0}} \tag{2}$$

where *J* is the flux through the membrane to the receptor compartment, *dQ* is the amount of drug across the membrane, *dt* is the permeation time (in seconds), and *A* is the diffusion area (in cm^2), calculated from the radius of the Franz cell, which was 1.77 cm^2. Note that J was obtained from the slope of the curve at

steady state. The apparent permeability (P_{app}) was calculated normalizing the flux (J) over the drug concentration in the donor compartment C_0.

2.2.4 Barrier effect studies

The barrier effect studies were performed with a Franz cell (Copley Scientific, United Kingdom), studying caffeine permeability through the membrane with respect to a negative and positive control. The untreated membrane was the negative control, while membrane covered with a Vaseline film was the positive one. The procedure was the same as the above-reported permeation studies with slight modifications: before filling the receiving chamber, in the donor, 200 mg of Vaseline (in the case of positive control) or 200 mg di PBS (in the case of negative control) was added over the membrane. In both cases, the added substances were left to equilibrate for 2 h before adding both the caffeine solution to the donor chamber and PBS to the receiving chamber (10.5 mL). Following this procedure, when applying the test to a real product, 200 mg of formulation can be spread over the membrane and the permeability data can then be compared with both the negative and positive ones. In all cases, the samples recovered from the receiving chamber were collected from 0 up to 3 h (0.5; 1.0; 1.5; 2.0; 3.0 h) and analysed by HPLC (Vanquish, Thermo-scientific, United States). The sampling volume was immediately replaced with the same volume of fresh PBS prewarmed solution at 37°C ± 0.5°C.

2.2.5 Membrane integrity

The membrane integrity was assessed by colorimetric assay using methylene blue dye. This procedure was applied at the end of each test (i.e., permeability, positive controls, negative controls, and barrier effect tests with the studied product). After the test, the donor chamber was washed with 2 mL of PBS (2 times) and 1 mL of methylene blue solution 0.05% was added. After 1 h, the receiving chamber samples were qualitatively evaluated, to confirm the colorlessness of the receiving solution. For comparative purposes, the test was also performed on a damaged model-like membrane (polymeric support without phospholipidic bilayer functionalization) in which the dye permeates, forming a blue receiving solution.

2.3 Statistical analysis

All experiments were performed in at least tripled independent replicates. Values are reported as means with standard deviation (SD) of the average value. Statistical analysis was performed using Microsoft Excel.

3 Results and discussion

3.1 Analytical method validation

The HPLC analytical methods for the quantification of caffeine and acyclovir were developed and validated by the determination of the following parameters: linearity, sensitivity, specificity, precision, and accuracy. The complete discussion, equations, figures, and dataset related to the analytical validation methods are reported in the Supplementary Material. In summary, the linear range for caffeine and acyclovir was 0.9–192 μg/mL and 0.1–50 μg/mL, respectively. Regarding the sensitivity, the limit of detection (LOD) of the analytical method was 0.028 μg/mL for caffeine and 0.01 μg/mL for acyclovir, while the limit of quantitation (LOQ) was 0.094 μg/mL for caffeine and 0.03 μg/mL for acyclovir. The methods specifically determined caffeine and acyclovir both in pure PBS solutions and in PBS with Aphthae gel. As a matter of fact, in both pure PBS and PBS with Aphthae gel, no interfering peaks that had the same retention time of caffeine and acyclovir were detected (Figure 1). Additionally, analyte chromatographic peak purity was confirmed by the analysis of the UV spectra recorded by DAD (data not shown). Lastly, precision and accuracy were evaluated by three replicate determinations of spiked samples at 80%, 100%, and 120% of the expected analyte concentration. The precision of the HPLC methods was determined as the percentage of relative standard deviation (RSD %, see equation (4S) in Supplementary Material) of the peak areas for replicate injections of the samples ($n = 3$ for each concentration). The mean RSD % for caffeine and acyclovir in pure PBS solutions were found to be 0.26% and 0.20%, respectively. On the other hand, the mean RSD % for caffeine and acyclovir with Aphthae gel in PBS solutions were found to be 0.09% and 0.11%, respectively. The obtained results indicated that the precision of analytical methods can be defined as acceptable, due to the RSD % of ≤2.0%. Additionally, the accuracy of the developed HPLC-UV methods was assessed *via* a recovery test. The mean Recovery % (see equation (5S) in Supplementary Material) of the analytical procedures for caffeine and acyclovir in PBS solutions were found to be 93.9% and 94.2%, respectively. On the other hand, the mean Recovery % of analytical procedures for caffeine and acyclovir with Aphthae gel in PBS solutions were found to be 97.6% and 109.7%, respectively. These results indicated that the accuracy can be defined as acceptable, owing to 80% ≤ % Recovery ≤120% for each concentration.

3.2 Experimental design and effect of biomimetic tissues

In accordance with Texeira and co-workers' permeability test (Teixeira et al., 2020), caffeine and acyclovir were tested over the intestinal artificial biomimetic membrane to replicate the permeability values obtained and to extend the test also to different membranes. Caffeine was selected beacause it is considered a very highly permeable substance caffeine is considered a very highly permeable substance and it is a reference standard for barrier effect studies. Conversely, acyclovir was taken as the lowest reference standard, being a low permeable drug. The test was performed using a Franz cell as a vertical diffusion cell and an intestinal biomimetic artificial membrane, prepared in accordance with that previously described by Corti et al. (2006a). Data obtained were compared to those in the literature to confirm the correct implementation of the experimental protocol and to validate the developed method, the reproducibility, and the validity of the artificial biomimetic membranes as well.

Caffeine and acyclovir permeability were evaluated through time and compared, resulting in a very high and very low apparent permeability value (30.5E-6 and 0.6E-6), respectively

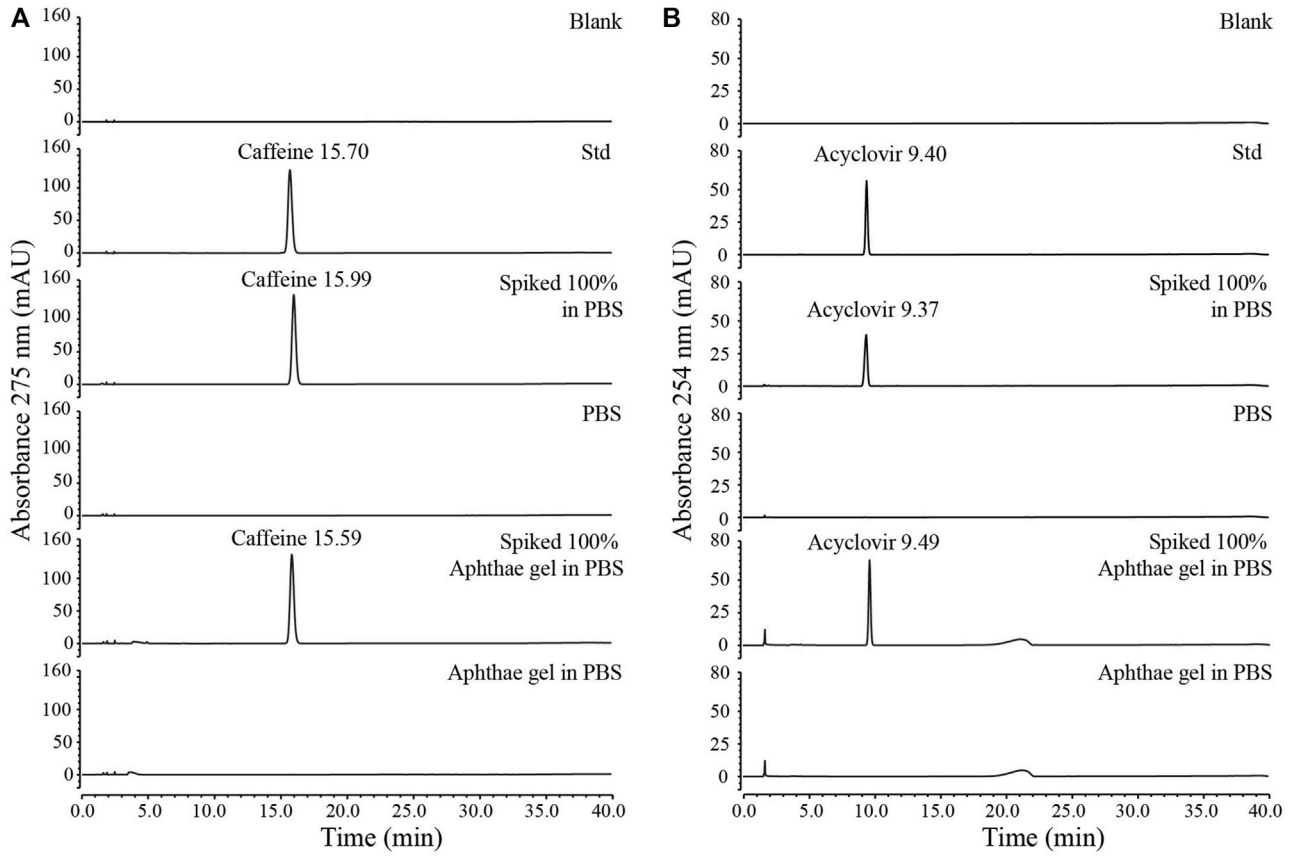

FIGURE 1
Specificity test for HPLC methods validation: **(A)** specificity test for caffeine HPLC method, **(B)** specificity test for acyclovir HPLC method.

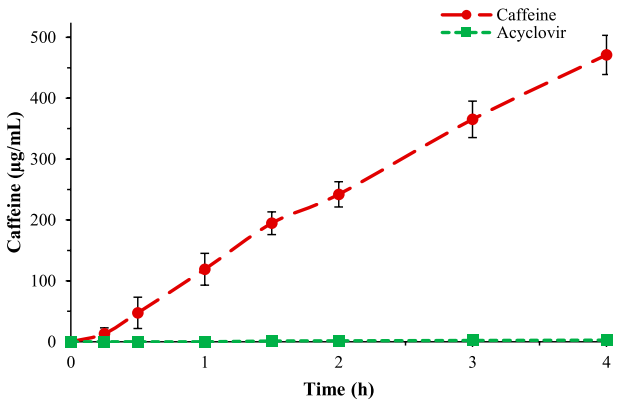

FIGURE 2
Comparison between caffeine (red) and acyclovir (green) permeability across the gastro-intestinal biomimetic membrane.

(Supplementary Table S15). The test was performed up to 6 h. The data obtained were plotted into a graph (Figure 2), in which it is possible to observe the differences between the behaviors of these two drugs across the gastro-intestinal membrane. In Supplementary Figures S3–S5, the HPLC spectra evolution over time, for caffeine and acyclovir, are shown respectively.

Another *in vitro* method to study the permeability of a compound consists of the use of cell-based methods. The ability of cells to create a barrier defines the ability of an assay to predict drug absorption. Several cell lines and culture systems were used to replicate a specific epithelium *in vivo* to predict drug absorption (Balimane et al., 2000). Monolayers have barrier properties (e.g., polarity, water interface, and tight junctions) under specific conditions that can be used for drug permeability experiments. Caco-2 are cells of human colon adenocarcinoma that exhibit many of the functional and morphological properties of the human intestinal enterocytes. They express a large part of the nutrient and drug transporter systems, as well as a portion of the metabolic enzymes expressed in the intestinal epithelium (Miret et al., 2004). The use of artificial biomimetic methods is a valid substitution to cell-based methods, and, in particular, several studies have compared the permeability of different drugs over both Caco-2 and intestinal biomimetic membrane, proving that, for those drugs that are transported just by passive diffusion (almost all drugs were absorbed by passive diffusion), the apparent permeability values can be comparable. To demonstrate this equivalence, the permeability data obtained in this study were also compared to Caco-2 permeability values (Yamashita et al., 2000; Zhu et al., 2002). In Table 1, the data obtained in this study were compared with Caco-2 and the Franz cell method literature data. The data obtained showed that the biomimetic membrane has a very similar permeability pattern in respect to cell-based tissue. Therefore, these simple and effective

TABLE 1 Comparison between experimental data and literature data.

	Franz cell (this study) cm/s	Franz cell (Teixeira et al., 2020) cm/s (E)	Caco-2 (Yamashita et al., 2000; Zhu et al., 2002) cm/s (E)
Caffeine	30.5E-6	36.2-6	30.8-6
Acyclovir	0.6E-06	0.40-6	0.3-6

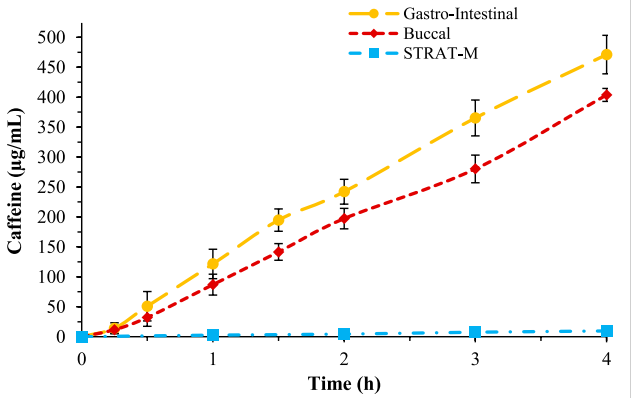

FIGURE 3
Comparison of caffeine permeability over gastro-intestinal membrane (yellow), buccal membrane (red), and STRAT-M® (blue).

biomimetic membranes can be used as a valid alternative for studying the permeability performance of active substances.

Once the method was validated, the caffeine permeability was evaluated over different biomimetic artificial membranes.

The buccal membranes were prepared following the indications of Mura et al. (2018). In detail, a lipidic ternary mixture composed of *n*-octanol, Lipoid®E80, and cholesterol was prepared and a cellulose acetate-nitrate membrane with pore size of 0.025 µm was impregnated and then used to perform the caffeine and acyclovir permeability tests. The tests were performed in the same conditions as the previous and the results showed that the buccal membrane is less permeable than the intestinal (Figure 3).

The same test was repeated also to study caffeine permeability across the skin, using the STRAT-M® biomimetic membrane. The conditions used for the transdermal permeability were different to the previous tests; the temperature of the skin test was 32°C and the test was performed studying caffeine permeability up to 24 h (Figure 3). The results showed that caffeine has a very low permeability across this membrane, in accordance with literature data.

In Table 2, the P_{app} values are reported, in which it is possible to observe that the gastro-intestinal membrane is the most permeable and the transdermal the least. The data obtained are in accordance with *in vivo* tests. In Figure 3, the percentage of permeated caffeine in all three different membranes were reported as a comparison, showing a significative difference of caffeine permeation between the membranes ($p < 0.05$). In Supplementary Figure S6, the HPLC spectra for caffeine over the three different membranes were compared.

Taking advantage of the implementation of these three different artificial membranes to evaluate caffeine permeability, the barrier effect method was developed to study the performance of SB-MDs over different biomimetic compartments.

TABLE 2 Caffeine permeability in different artificial biomimetic membranes.

	Gastro-intestinal	Buccal	Dermal
P_{app} x10^{-6} cm/s	25.3	18.2	0.5

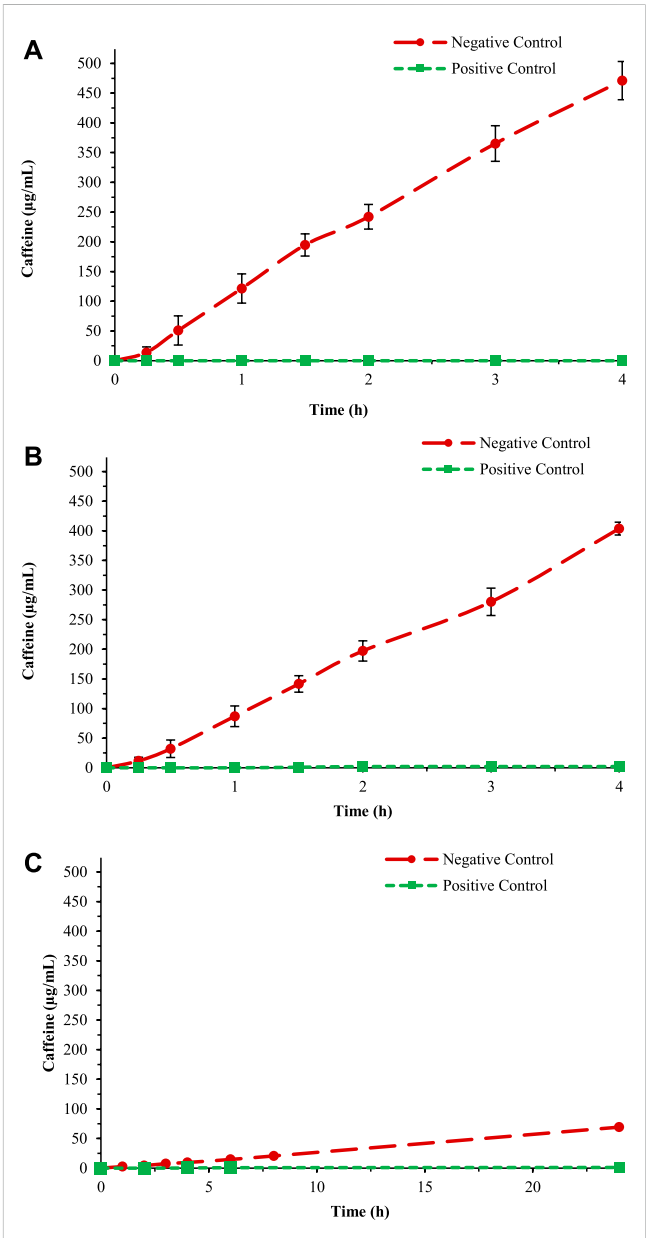

FIGURE 4
Negative and positive control test for the three different membranes: **(A)** Gastro-intestinal, **(B)** Buccal, and **(C)** STRAT-M®.

TABLE 3 Aphthae gel—Concentration data of the caffeine passage.

Time	Average data with SD
[h]	[μg/mL] ± Δ_{Conc}
0	0.000 ± 0.000
0.5	5.497 ± 0.572
1	22.270 ± 2.954
1.5	40.119 ± 3.488
2	66.443 ± 2.546
3	109.700 ± 3.782
Membrane integrity test	**Compliant**

3.3 Barrier effect studies

3.3.1 General protocol design

The barrier effect is an *in vitro* test useful to determine the performance of a medical device and permit identification of their film-forming ability. For the *in vitro* test, caffeine was selected as a probe to assess the propensity of a given product to form a protective film due to its ability to permeate different models of human tissues (i.e., intestinal, buccal, and cutaneous) even in absence of damage. The barrier effect test consists of studying the caffeine permeability over an artificial biomimetic membrane covered by the SB-MD and comparing the permeability with a positive and negative control. For the positive control, the biomimetic membrane was covered with Vaseline, a substance able to create a strong protective film, through which caffeine is not able to pass. For the negative control, the permeation of caffeine was evaluated after treating the membrane with PBS solution (Figure 4). The complete positive and negative control dataset together with chromatograms are reported in Supplementary Tables S16–S18 and Supplementary Figures S7–S9.

For the formation of the protective film over the membrane, the substance was left for 2 h before the barrier effect test started. All tests were done five times to evaluate the reproducibility and accuracy of data. At the end of each test, the integrity of the membrane was evaluated: the presence of colourless receiving solution indicated the absence of damage in the membrane structure and, therefore, a significative permeability data.

The method as developed will permit the evaluation of the barrier effect of SB-MDs. With this aim, caffeine permeability across the "untreated" membrane may be normalized as 100%, and the difference in terms of caffeine permeability in respect to both negative and positive controls (as described above) will numerically measure the film-forming ability of the formulation based on the substances under examination. The pattern of the protocol is shown in Supplementary Figure S10.

3.3.2 Case study: Barrier effect of aphthae gel

Aphthae gel is an experimental gel-like SB-MD under study for the treatment of aphthae, stomatitis, and microlesions of the mouth and which, besides the excipients, contains xyloglucan, aloe vera extract, vegetal natural glycerol, and polyvinylpyrrolidone (PVP K30) as active ingredients. All these functional components have hydrating, protective, lenitive, and adhesive properties, as well as film-forming ability (Nair, 1998; Sharma et al., 2014; Esquena-Moret, 2022). Herein, the barrier effect of Aphthae gel was determined by applying the protocol developed. To test the product, the absorption of caffeine was evaluated across a synthetic biomimetic buccal membrane treated with 200 mg of Aphthae gel. The test was done in triplicate to evaluate the reproducibility and accuracy of data. In Table 3, the average data with SD are reported.

To calculate the reduction of caffeine passage, the values at 3 h were plotted into a histogram in comparison with the positive and negative control (as above described). The percentage of caffeine in the negative control obtained using the buccal membrane (data reported in Figure 4B) has been considered 100% (Figure 5).

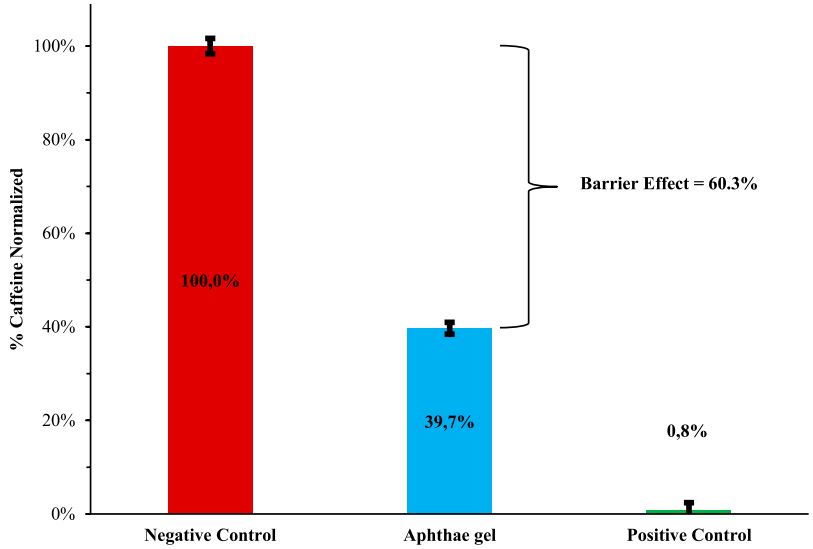

FIGURE 5
Barrier effect of Aphthae gel—comparison between value at 3 h of experiment.

After treatment with Aphthae gel, a reduction of 60.3% in caffeine permeability across a biomimetic membrane was observed.

4 Conclusion

This study had the goal of developing a standard barrier effect procedure useful to evaluate the film-forming ability of SB-MDs as a part of the experimental process necessary to establish the safety and effectiveness of the products in response to the new European regulations and in accordance with animal welfare aspects (principle of the 3Rs).

With this aim, in a first validating approach, the permeability of model drugs (caffeine and acyclovir) was studied over biomimetic membranes (simulating gastro-intestinal, buccal, and skin tissues). The results obtained were compared with literature data confirming a) the correct implementation of the experimental protocol, and b) the procedure of the artificial biomimetic membrane. The results of the study of the lipid-impregnated membranes replicated the data obtained from the literature, showing a significative difference in terms of caffeine permeability between the three different biomimetic membranes. The gastro-intestinal support showed an apparent permeability higher than both buccal and skin, as expected. In the second part of the study, we demonstrated that these simple and effective biomimetic membranes may be successfully exploited to develop a barrier effect *in vitro* test to evaluate the protecting performance of substance-based medical devices (SB-MD). The protocols here proposed were designed by comparing the ability of a SB-MD to reduce the permeation of caffeine through a tissue (pre-covered with the product under examination), with positive (untreated tissue) and negative (tissue covered with Vaseline) controls. The barrier effect was expressed as the difference in terms of caffeine permeability between negative controls (normalized as 100%) and the SB-MD. The designed *in vitro* test was then applied to Aphthae gel, an experimental gel-like SB-MD under development and herein used as a case study. The results showed that the product reduces caffeine permeability across a biomimetic buccal membrane by about 60.3%. This data highlights the capability of Aphthae gel to protect the mucosae. Overall, the results of this study show that biomimetic membranes represent a useful tool for the preliminary high throughput screening of film-forming formulation candidates to be further tested for their efficacy and safety in clinical trials, as requested by the regulations related to substance-based medical devices (SB-MD). Concluding, this work provides scientifically validated procedures which may contribute to the creation of standard methods to assess the biological evaluation of medical devices.

Data availability statement

The original contribution presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

EA: conceptualization, supervision, and review and editing. RB and SP: formal analysis, data curation, and writing—original draft preparation. SZ, DN, and WB: provided approval for publication of the content.

Conflict of interest

RB, SP, EA, SZ, DN and WB were employed by Labomar S.p.a.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fdsfr.2023.1124873/full#supplementary-material

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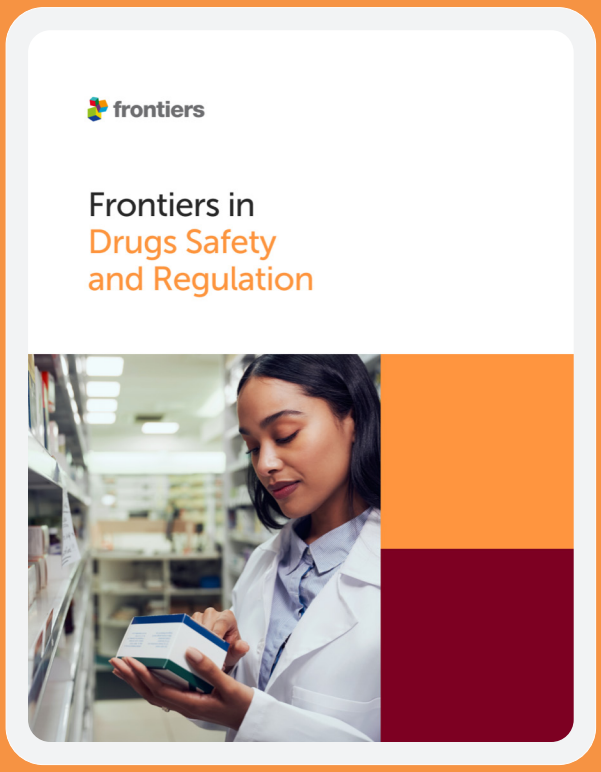

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