**Supplemental file 1: Practical methodology of metabolic therapies used by integrative physicians**

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| **Treatments** | **Route of administration** | **Techniques** | **Authors** | **Study Design\*\*** | **Key Findings** | **Level of evidence\*\* and remarks** |
| Sodium bicarbonate applications (NaHCO3) | Oral | 1 Teaspoon of NaHCO3 mixed in 500 ml of water | Estrella V et al1  Robey IF et al2  Robey IF et al3  Pötzl J et al4  Raghunand N et al5  Faes S et al6  Pilon-Thomas S et al7  Abumanhal-Masarweh H et al8  Takeda Y et al9  Yamazaki K10  Ding B et al11  Gillies RJ et al12 | Preclinical  Preclinical  Preclinical  Preclinical  Preclinical  Preclinical  Preclinical  RCT  NRCT  Preclinical  RCT | NaHCO3 inhibits tumor growth by raising the peritumoral pH.1  Reduce tumor metastases2  Inhibit the tumor invasion and increase the survival period.3  NaHCO3 upregulate natural killer (NK) cells function by which it delays tumor growth.4  NaHCO3 enhances the effectiveness of chemotherapy.5  Reduces the tumor angiogenesis.6  NaHCO3combined with immunotherapy had modest or no effect on tumor growth.7  NaHCO3exhibit anti-carcinogenic activity and improves the efficacy of cancer drugs.8  NaHCO3does not improve the efficacy of chemotherapy drugs.9,10  NaHCO3alkalizes the tumor microenvironment, regulates lactic acid metabolism, and enhances the effects of immunotherapy.11  No significant anti-carcinogenic effect except reduction in cancer-related pain.12 | **Level C (II)**  The clinical trials have smaller sample size and majority of the evidence are from in vitro or vivo studies. |
| Nasal | 1 ml of NaHCO3 with 4 ml of normal saline (NS) over 15 minutes |
| Intravenous | 50 ml of NaHCO3 with 30 ml of vitamin C in 450ml of NS administered over 90 minutes |
| Vitamin C | Oralꭍ | Liposomal vitamin C drink (200 ml) taken 3-4 times a day. | Fritz H et al13  Sebastian S et al14  Polireddy K et al.15  Mohseni S et al16  Nielsen TK et al.17  Hoffer LJ et al18  Schoenfeld JD et al19  Ou J et al.20  Ou J et al.21 | SR  NRCT  RCT  SR  CT  RCT RCT  RCT  RCT | High dose Vitamin C(HVC) tumor mass and improve survival in combination with chemotherapy.13  HVC exerts anti-inflammatory effects on cancer cells by reducing levels of CRP and ESR.14  Depletion of cellular NAD+ in cancer cells, as opposed to normal cells, leads to reduced ATP levels and significantly increases α-tubulin acetylation in cancer cells.15  HVC may have positive effects on cancer survival.16  No significant effect on cancer cells.17  HVC enhances the impact of chemotherapy and facilitates disease control and remission.18, 19  HVC improves quality of life and survival rate when combined with complementary therapies.20,21 | **Level B (I)**  Even though RCTs suggest the efficacy of vitamin C in cancers, systematic reviews indicate inconclusive evidence for making a recommendation and call for further robust trials. |
| Intravenous | 7.5 to 100 gms of vitamin C (depends on weight of patient ie.,1.5gms/kg of weight) |
| CO-Q 10 enzyme | Oralꭍ | 25mgs/day | Roffe L et al22  Dadali T et al23  Hu C et al24  Tafazoli A25  Fouad AA et al26  Abdel‐Latif et al27  Frontiñán-Rubio J et al28  Lockwood K et al29 | SR  Preclinical  Preclinical  SR  Preclinical  Preclinical  Preclinical  CT | Coenzyme Q10 (CoQ10) may help in improving the cancer treatment outcomes.22  Delivering oxidized Coenzyme Q10 to boost the mitochondrial Q-pool increases ROS, enhancing anti-cancer effects.23  CoQ10 exhibited an inhibitory effect on cell proliferation, as well as on migration and invasion of cancer cells.24  Coenzyme Q10 can target the mechanisms underlying breast cancer tumor progression.25  CoQ10 reduces lipid peroxidation, maintains glutathione and superoxide dismutase activity, and decreases tumor necrosis factor-α and nitric oxide levels.26  CoQ10 reduces cell proliferation, histological changes, AFP and TNF-α levels in hepatocellular carcinoma by altering lipids, CD59 expression, and phospholipase D activity.27  CoQ10 modulates the angiogenesis, and monocyte infiltration.28  CoQ10 offers tumor regression in breast cancer.29 | **Level C (II)**  Although there are systematic reviews suggesting the usefulness of CoQ 10 in cancers, all the systematic reviews discusses evidence from preclinical studies, except for one clinical trial. |
| Keto Diet |  | The ketogenic (keto) diet is a high-fat, low-carbohydrate diet, where carbs are limited to about 5-10% of daily caloric intake, 70-75% of daily calories come from fats, and 20-25% of daily calories from protein. | Zhao H et al30  Romer M et al31  Yang YF et al32  Klement RJ et al33  Klement RJ et al34 | SR & MA  SR  SR & MA  RCT  RCT | There were no significant changes in IGF-1 and TNF-α related to tumor growth.30  No conclusive evidence for anti-tumor effects.31  Inadequate evidence to support the beneficial effects of keto diet on antitumor therapy.32  The keto diet influences several metabolic health biomarkers, including lowering gamma-glutamyl-transpeptidase (GGT) and the triglyceride-glucose index, while improving the HDL cholesterol/triglyceride ratio and free T3 levels.33  Improvement in metabolic parameters such as gamma-glutamyl-transpeptidase (GGT) and the triglyceride-glucose index.34 | **Level C (I)**  Current studies suggest that the keto diet is a promising intervention for modulating the tumor microenvironment. However, considering the inconclusive evidence suggested by the meta-analysis and systematic reviews, more research with larger sample sizes and different cancer types is needed. |
| **Ozone Therapy**  Major Autohaemotherapy  Minor Autohaemotherapy  Rectal insufflation  Ear insufflation  Ozone Bagging | Intravenous  Intramuscular  Rectal  Otic  Topical  Intravenous  Nasal | Ozone concentration used in this procedure is between 20-40 μg/ml and 200 ml of blood is mixed with equal quantity of ozone oxygen mixture.  In this procedure, ozone is mixed with 2-3 ml of blood and is mixed with 5ml of ozone at 20-30 μg/ml concentration and injected intramuscularly.  Ozone oxygen mixture 10-40 μg/ml concentration is introduced through rectum via a catheter.  Ozone is introduced through the ear at a concentration varying from 10-30 μg/ml over 5 minutes.  The patient’s body is exposed to ozone after fully covering the desired body part with a polythene cover. The dose concentration ranges from 10 to 60 μg/ml.  Up to 2 litres of the patient's blood is drawn using sterile techniques. An anticoagulant is added to the blood to prevent clotting during the procedure. The drawn blood is mixed with an equal volume of the ozone-oxygen mixture (10 to 60 μg/ml concentration). This process is performed using specialized equipment to ensure thorough and sterile mixing. The ozonated blood is then slowly reinfused back into the patient.  Ozone at a concentration of 15 μg/ml is bubbled in a vegetable oil and then through a nasal cannula over 15 minutes. | Baeza-Noci J et al35  Clavo B et al36  Clavo B et al37  Yıldırım M et al38  König B et al39  Tang S et al40  Simonetti V et al41 | SR  CT  Review  Preclinical  CT  Preclinical  Preclinical | Ozone's use in cancer treatment requires more preclinical research across various cell lines and dosages, as responses vary among cancer types.35  Ozone therapy attenuates tumor hypoxia.36  Ozone demonstrate benefits as an adjuvant therapy to chemotherapy and radiation.37 Ozone therapy inhibits proliferation of breast cancer cells.38  Ozone therapy positively modulates the mitochondrial bioenergetics.39  Ozone induces apoptosis in hepatocellular carcinoma models through intrinsic mitochondria-dependent pathway.40  Ozone modulates the inflammatory path way and tumor microenvironment in melanoma models.41 | **Level C (II)**  Most of the evidence are from preclinical studies and reviews except for few single group studies. |
| Hyperbaric ozone  Breathing ozone through oil |
| Hydrogen peroxide | Nasal | 0.3 ml of 1% H2O2 with 3ml of NS over 15minutes. | Nimalasena S et al42  Chua PJ et al43  Vilema-Enríquez G et al44  Kemmotsu N et al45  Mundi N et al46 | RCT  Preclinical  Review  Preclinical  Case series | H2O2along with radiation therapy offers complete/partial tumor response.42  H2O2 induces cell cycle arrest by modulating the oxidative stress related genes in breast cancer cells.43  H2O2 exhibit apoptopic, anti-inflammatory, anti-oxidative properties and may works as a therapeutic tool in treating cancers.44  H2O2 reduces non-irradiated tumor growth.45  H2O2 reduces the tumorlesion size in non-melanoma skin cancer.46 | **Level C (II)**  The evidences are majorly from preclinical studies except for one RCT and a case series. Further studies are recommended. |
| Molecular Hydrogen therapy | Nasal  Oral | Hydrogen inhalation over 30-60minutes/day  Given in the form of hydrogen rich water | Mohd Noor MNZ et al47  Chen J et al48  Chen JB et al49  Chen JB et al50  Chen JB et al51  Chen JB et al52  Runtuwene J et al53  Asgharzadeh F et al54 | SR  Case report  CT  RCT  RCT  Case report  Preclinical  Preclinical | Hydrogen (H2) shows promise as a standalone or adjunct therapy, improving survival, quality of life, blood parameters, and tumor reduction.47  H2 inhalation increases survival time and offers complete remission of brain tumor.48  H2 inhalation demonstrated significant complete and partial remission of advanced cancers.49  H2 therapy attenuates the tumor progression.50  H2 therapy enhances the immunosenescence of advanced non-small cell lung cancer cells.51  H2 therapy induces reduction in tumor size in gall bladder cancer.52  H2 water inhibits colon cancer by enhancing cellular apoptosis.53,54 | **Level B (II)**  The literature suggests moderate evidence from clinical trials which warrants the use of molecular hydrogen therapy as a promising anti-tumor intervention. However, large scale studies are warranted. |
| Acupuncture |  | Acupuncture points are chosen based on the Traditional Chinese Medicine principles and are changed over the course of treatment based on the patient’s response and progress. | Lou H et al55  Li Jinxia et al56  Zhao Yu et al57  Li Hongjin et al58 | Preclinical  CT  SR & MA  CT | Acupuncture promotes mitochondrial biogenesis and reduces oxidative stress.55  Acupuncture inhibits the Leptin/AMPK signaling pathway and reduces mitochondrial DNA mutations. 56  Acupuncture reduces oxidative stress.57  Acupuncture induces changes in several metabolites, including glutathione disulfide, phosphorylcholine, 6-methylnicotinamide, glutathione, and putrescine. 58 | **Level B (II)**  Even though the evidence suggests acupuncture to have an impact on the metabolism, more robust studies are required to establish level A evidence. |
| Yoga therapy | This involves use of different yogic postures, breathing and, meditation techniques. | Ding et al59  Banasik et al60  Moraes et al61 | MA  RCT  SR | Yoga can reduce the level of salivary cortisol and DNA damage.59  Yoga therapy reduces cortisol levels.60  Yoga and meditation helps to reduce stress hormones such as cortisol, epinephrine and nor epinephrine.61 | **Level B (II)**  While evidence suggests yoga reduces stress, more robust studies are needed to confirm its direct impact on cancer metabolism and related pathways. |
| Medical Cannabis | Sublingual | The products used with a high CBD (Cannabidiol) and low THC (Tetrahydrocannabinol) component. The initial dose is 5-10 mg of CBD, adjusted as needed. | Twelves C et al62  Bunsick DA et al63  Hinz B et al64  Rybarczyk A et al65  Ivanov VN et al66 | RCT  Review  Review  Review  Preclinical | Cannabis exhibits anti-tumor response and increases the survival rate in glioblastoma.62  Cannabis induces epigenetic modulation of cancer metabolism and there by prevent its progression and metastasis.63  Cannabis, through cannabinoid pathways, suppresses tumor cell growth, invasion, metastasis, angiogenesis, and chemoresistance, while promoting apoptosis and autophagy.64  Cannabinoids demonstrate anti-tumor and anti-inflammatory effects, modulating multiple signaling pathways, including Nrf2.65  Cannabinoids combined with radiation therapy induces cancer cell death.66 | **Level C (V)**  Majority of the evidence comes from the expert reviews of preclinical studies. Well-designed human trials are warranted. |

*\*\*MA- Meta-analysis; SR- Systematic review; CT- Clinical Trials; RCT- Randomized control trials; NRCT- Non-randomized control trials.*

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| ***\*\*Level of evidence*** | ***\*\*Strength of evidence*** |
| *I- High quality systematic review, meta-analysis and randomized control trials.*  *II- Lesser quality systematic review, meta-analysis and randomized control trials.*  *III- Observational studies*  *IV- Case reports and case series*  *V- Experts opinion (review/opinion/perspectives)* | *A- Strong evidence, the recommendation is primarily based on level I and II studies, requiring at least one level I study.*  *B- Moderate evidence, The recommendation is based on either a high-quality randomized controlled trial or a majority of level II studies, including those with short follow-ups and small sample sizes.*  *C- Weak evidence, The recommendation is based on just one level II study.*  *D- Conflicting/No Evidence, Level I and II studies either conflict in their conclusions or fail to demonstrate any benefit.* |

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