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Research Paper

Review on omega-3 fatty acid in relation to DHA Docosahexanoic acid

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I. Introduction

Docosahexaenoic acid (DHA) is a long-chain, highly unsaturated omega-3 (n-3) fatty acid. It has 22 carbons in its acyl chain, which includes 6 double bonds. Chemically it can be described as all-cis-4,7,10,13,16,19-docosahexaenoic acid, with the numbers 4, 7, 10, 13, 16 and 19 referring to the carbon atoms in the acyl chain that bear double bonds when the carboxyl or α-carbon is counted as number 1 (Fig. 1). DHA is shown in the common fatty acid nomenclature as 22:6ω-3 or 22:6n-3, with the ω-3 (or n-3) indicating the position of the first double bond in the acyl chain, in this case counting the methyl or ω-carbon as number 1 (Fig 1). The common name for DHA, which is rarely used, is cervonic acid. Fatty acyl chains with no double bonds, such as in saturated fatty acids, are straight and pack together tightly. Introduction of a cis double bond into an acyl chain introduces a ‘kink' into the chain, making it less easy for such chains to pack together and lowering their melting point. As the acyl chain of DHA contains 6 cis double bonds, it becomes highly twisted (fig. 1), giving it unique physical properties and resulting in a very low melting point (-44°C). DHA is metabolically related to other n-3 fatty acids. It can be synthesized from the plant-derived α-linolenic acid (ALA; 18:3n-3) or obtained directly from the diet. In common with other fatty acids, DHA is most often found linked via its carboxyl group into a more complex lipid structure such as a triglyceride, phospholipid or cholesteryl ester. Here, the pathway of DHA biosynthesis, dietary sources of DHA, the status (i.e. concentration) of DHA at different sites in the human body and the response of those sites to increased DHA intake, and selected actions of DHA at the molecular and cellular levels will be described. DHA plays vital roles in the structure and function of the brain and eye and an appropriate supply during fetal life and in infancy is essential to assure optimal development.

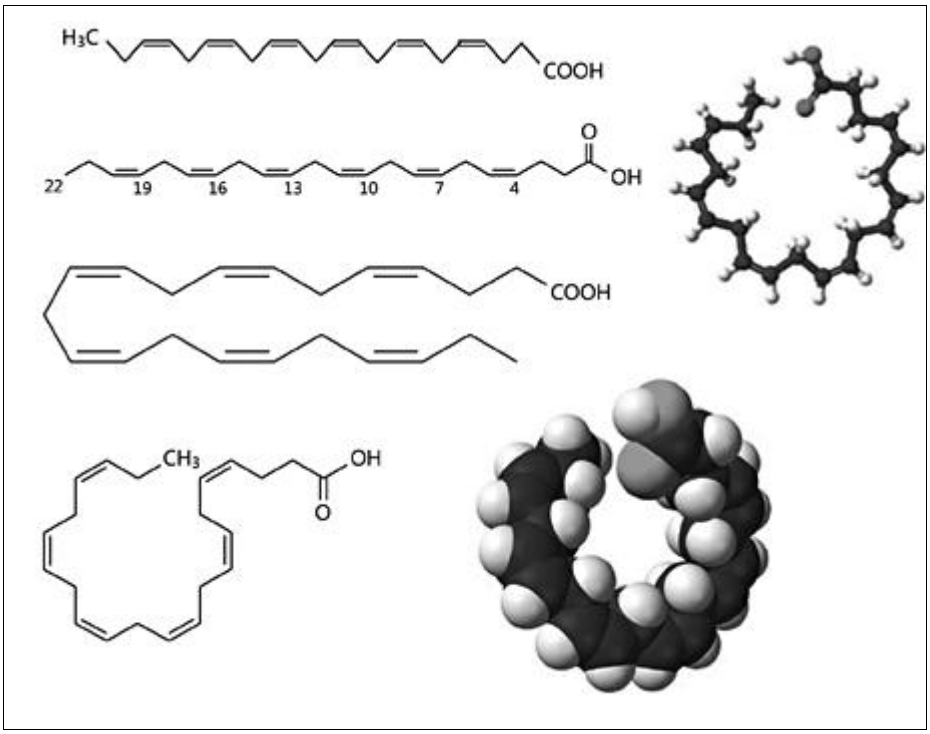

Fig 1: Different depictions of the structure of DHA. DHA has 22 carbons and 6 cis double bonds in its hydrocarbon (acyl) chain. The α-carbon is the carbon of the terminal carboxyl group (COOH) and the ω-carbon is the carbon of the terminal methyl (CH3) group.

Biosynthesis of DHA

ALA is an essential fatty acid. It is synthesized in plants and in many lower organisms and is found in the human diet mainly as a component of green leaves, some nuts, seeds and vegetable oils, and foods made from or containing those ingredients. There is a metabolic pathway that links ALA to DHA (Fig. 2). This pathway involves a series of enzyme-catalysed elongation and desaturation reactions. Elongation enzymes, called elongases, add pairs of carbon atoms to the growing acyl chain, in this case converting an 18-carbon fatty acid into a 22-carbon one, while desaturase enzymes insert double bonds into the acyl chain, in this case converting a fatty acid with 3 double bonds in its acyl chain into one with 6 double bonds. These reactions occur predominantly within the endoplasmic reticulum. The pathway is believed to mainly occur within the liver, but there is some evidence that other tissues, including brain and testis, have high expression of the genes encoding the relevant enzymes.

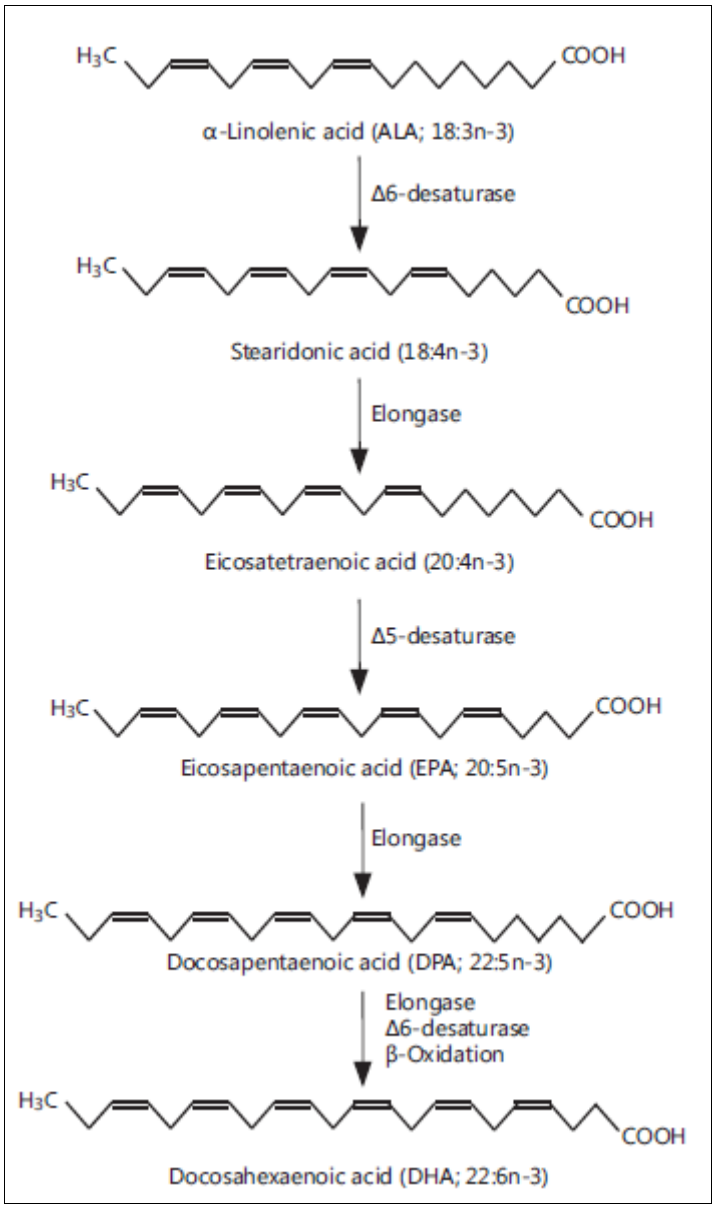

Fig 2: The metabolic pathway of conversion of α-linolenic acid to DHA showing the enzymes involved.

The initial step in the pathway is the conversion of ALA to stearidonic acid (18:4n-3), catalysed by Δ-6-desaturase, which is generally considered to be the rate-limiting reaction in the pathway. Δ-6-desaturase is encoded by the gene fatty acid desaturase 2 *(Fads2)*. Stearidonic acid is converted to 20:4n-3 by the addition of 2 carbons by the enzyme elongase-5, encoded by fatty acid elongase 5 *(Elovl5)*. 20:4n-3 is then converted to eicosapentaenoic acid (EPA; 20:5n-3) by insertion of a double bond catalysed by Δ-5-desaturase, which is encoded by the gene fatty acid desaturase 1 *(Fads1)*. EPA can be elongated by elongase 2 (encoded by *Elovl2*) to form n-3 docosapentaenoic acid (DPA; 22:5n-3) and then to 24:5n-3 followed by desaturation that again uses Δ-6-desaturase activity to form 24:6n-3. This desaturation seems to be catalysed by the same Δ-6-desaturase as in the first step of the pathway. 24:5n-3 is then translocated from the endoplasmic reticulum to the peroxisome where it undergoes one round of β-oxidation to form DHA.

It is important to note that the same enzymes are active in the metabolism of the n-6 fatty acid family, converting the essential n-6 fatty acid linoleic acid (18:2n-6) to arachidonic acid (20:4n-6) and on to n-6 DPA (22:5n-6). Thus, competition exists between the conversion of n-6 and n-3 fatty acids. The rate-limiting enzyme, Δ-6-desaturase, has a preference for ALA over linoleic acid. However, this may be more than offset by the greater abundance of linoleic acid than ALA in most human diets, meaning that the metabolism of the former is favoured.

In addition to the availability of the essential fatty acid substrates and the competition between them, a number of other factors have been demonstrated to regulate the pathway. These include the availability of

several trace elements including zinc and iron, since the enzymes involved in the pathway require these as co-factors; sensitivity to insulin; female sex hormone status; polymorphisms in *Fads* genes which control gene expression and enzyme activity, and epigenetic modification of *Fads* and *Elovl* genes, which will affect their expression. Other nutrients, metabolites and hormones, and ageing may also affect the pathway. Measurements of EPA and DHA status reveal differences among some population subgroups, for example between men and women [1]and among individuals with different *Fads* polymorphisms [2], that are likely to reflect different activities of the biosynthetic pathway. There has been much interest in the reported differences in EPA and DHA status between men and women. Studies using stable isotopes to trace metabolism of ALA have demonstrated that the conversion of ALA to both EPA and DHA is more efficient in young women than in young men.[3] In men, conversion of ALA to EPA has been reported to be between 0.3 and 8%, and conversion to DHA <1%, whereas in women up to 21% conversion to EPA and up to 9% conversion to DHA have been reported. It has been suggested that the higher rate of conversion in women may be because of their greater requirement to produce DHA during pregnancy and lactation. Infants may be more effective at converting ALA to DHA than adults, and newborns appear to be better at synthesizing DHA than older infants.[4]

Sources of DHA

Since neurons do not have a de novo DHA synthesis system, the supply of DHA to neurons depends on diet or synthesis from the DHA precursor α-linolenic acid.[5] Previous studies have shown that DHA is found in animals, fungi, and many microorganisms, and is particularly abundant in fish oil.[6] Oils such as menhaden, salmon, sardines, and cod liver are abundant in DHA.[7] Vegetable oils such as linseed oil, canola oil, and soybean oil, chia, cannabis seeds, and walnuts, are abundant in α-linolenic acid, a precursor of DHA, and it is converted to EPA and DHA in the human body.[8] Earlier studies have shown that high intake of α-linolenic acid in humans increased the EPA content in plasma lipids, red blood cells, white blood cells, platelets, and breast milk, but did not increase DHA.[9]

Algal oil provides a substitute for fish and fish oil. It's an oil made from certain types of microalgae. Usually, fish consume these microalgae and convert them into essential fatty acids that get stored in their tissue, which you eat. Algal oil skips the fish altogether. Algal oil contains docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). DHA and EPA are two of the most important omega-3 fatty acids. Algal oil also contains other important fatty acids called omega-9 fatty acids.

DHA Status

DHA Concentration in Different Metabolic and Anatomical Compartments

DHA is transported in the bloodstream as a component of lipoproteins (within triglycerides, phospholipids and cholesteryl esters) or as a nonesterified ('free') fatty acid (largely due to release from adipose tissue stores or from spill-over of lipase-mediated hydrolysis of circulating lipoproteins). DHA can be stored in adipose tissue esterified into triglycerides. DHA is found in all cell membranes esterified into phospholipids and other complex lipids.

DHA is highly concentrated in the Human Brain and Eyes

More than 50% of the dry weight of the human brain is lipid, particularly structural lipid (i.e. phospholipids). The most abundant fatty acids in the brain are DHA, arachidonic acid and adrenic acid.[10] The human brain and retina contain an especially high proportion of DHA relative to other tissues and little EPA.[11] For example, DHA was reported to contribute an average of 18% of fatty acids to adult human brain grey matter, while Makrides et al.[12] reported average DHA contents of about 8 and 12% of fatty acids for human infant cerebral cortex and retina, respectively.

DHA Concentration during Pregnancy

There is a significant linear relationship between the DHA contents of maternal and umbilical cord plasma phospholipids. This suggests that maternal plasma phos- pholipids are an important source of DHA for the fetus and that maternal plasma phospholipid DHA concentration determines DHA supply to the fetus. An increase in maternal plasma DHA concentration occurs during pregnancy, and this increase precedes the increase in DHA accretion by the brain.[13]

Docosahexaenoic acid in breast milk: Impact on infant brain development

The long chain omega-3 fatty acid, DHA, is a major lipid in the brain recognized as essential for normal brain function. n infants, DHA is important for optimal visual and cognitive development. The usual intake of DHA among toddlers and children is low and some studies show improvements in cognition and behavior as the result of supplementation with polyunsaturated fatty acids including DHA.

Due to the lack of de novo PUFA synthesis, the rate of membrane DHA incorporation in early life—in the brain as well as in other tissues—depends on maternal transfer, dietary supply (i.e., breastfeeding) and endogenous LC-PUFA production

More recently, a large cluster randomized trial of breastfeeding promotion using an experimental design demonstrated a large effect of breastfeeding on cognition, adding credence to the evidence for beneficial effects seen in past observational studies.[14] Anderson et al.[15] showed in a meta-analysis that, after appropriate adjustments, breastfeeding was associated with an advantage of around three points on tests of cognition in children born at term and around five points in those born preterm, both large effects in population terms. The implication is that, over and above social factors, one or more constituents of breast milk benefit neurodevelopment, particularly so in those born preterm, at a more sensitive stage of brain development.

DHA and depression

Brain needs the type of fatty acids that are in omega-3s for proper functioning. It's believed by some that those who experience depression may not have enough EPA and DHA. This is the premise that researchers are using as they study the possible benefits of using omega-3 and fish oil to treat depression.

In 2009 researchers reviewed data from three studies that used EPA in the treatment of three different types of depression: recurrent major depression in adults, major depression in children, and bipolar depression. The large majority of subjects taking EPA in all types showed significant improvement and benefited from the EPA as compared to those with a placebo. An overview of research on omega-3s and depression showed that DHA may also play an important role along with EPA in the treatment of various types of depression. Those with minor depression, postpartum depression, and suicidal ideation had lower levels of EPA and DHA. These studies showed that a combination of EPA and DHA found in fish oil seemed to improve the depression symptoms of most participants that were tested.[16]

Biological functions of DHA

Antioxidant activities of DHA

Although it is a highly polyunsaturated fatty acid, astonishingly, DHA can act as an antioxidant. Oral administration of DHA was accompanied with an increase in the antioxidant activities, such as catalase, glutathione peroxidase (GPx) and glutathione reductase (GR) enzyme activities. [17] There are also a few reports of the effect of DHA on the genetic expression of antioxidative enzymes. DHA increases expression of GPx in the brain hippocampus. Dietary polyunsaturated fatty acids also increase the mRNA levels of catalase and glutathione peroxidase in hepatic tissues.[18] Finally, DHA being a member of the highly unsaturated fatty acid family can act as an antioxidant even in the oxidatively vulnerable organs including the brain

Antihypertensive effects

Epidemiological study indicated plasma docosahexaenoic acid (DHA) level as a useful biomarker of the frequency of fish intake.[19] The intake of fish oils has been associated with a significant reduction in blood pressure (BP), triglycerides, and very-low density lipoprotein cholesterol.[20] The effect of fish oil on reducing heart rate (HR), a CVD risk factor, has also been recognized.[21] In a Scottish study, 2 g of DHA decreased the systolic and diastolic blood pressure and heart rate significantly as compared to the placebo. Further, the high-density lipoprotein cholesterol (HDL-C) increased significantly, and total cholesterol (TC)/HDL-C and non-HDL-C/HDL-C ratios decreased significantly in DHA treated groups. [22]

DHA improves memory

The hippocampus and the cerebral cortex are referred to as the key structures of memory formation. Gamoh et al.[23] in their study DHA (300 mg/kg/day, for 10 weeks) fed to male Wistar rats (tested by radial maze tasks and/or active shuttle avoidance apparatus) significantly ameliorated learning-related memory in DHA-deficient rat groups. Although the mechanism is unclear, corticohippocampal enrichment of DHA was positively correlated with improvement of memory.[24] Lim and Suzuki,[25] also reported that dietary administration of DHA to young mice for 4–7 months improved their spatial cognition learning ability

Effects of DHA on neurogenesis and improvement of memory

The dentate gyrus is a part of the hippocampus and is critical for forming/storing spatial memories. It is one of the regions in the brain where neural progenitor cells constantly produce new neurons (i.e. undergo neurogenesis), which then integrate into the new neural network and form new synapses with other numerous neurons. Although the exact mechanisms remain unknown, neurogenesis is believed to participate in learning and memory.[26]

Neural stem cells (NSCs) isolated from 15.5-day-old rat embryos were propagated as neurospheres and cultured with or without DHA for the periods of 4 and 7 days. DHA significantly elevated the number of Tuj1-positive neurons when compared with that of the control on both 4 and 7 culture days, and the newborn neurons in the DHA group were morphologically more mature than those in the control. Thus, DHA stimulates the differentiation of neural stem cells into neurons by helping the exit from cell cycle and suppressing the cell death.[27]

Effects of DHA on Alzheimer's disease

Docosahexaenoic acid (DHA) is an omega-3 fatty acid identified as a potential treatment for Alzheimer disease. Epidemiological studies have shown that omega-3 fatty acid consumption reduces Alzheimer disease risk and DHA modifies the expression of Alzheimer-like brain pathology in mouse models. Previous studies investigated the effect of oral administration of DHA on cognitive impairment of Aβ-infused AD model. After 12-week oral administration of DHA, increases in brain DHA levels were significantly associated with amelioration of learning-related memory of the rats. These results provided us with an ample opportunity to study the effect of DHA in AD model rats maintained in DHA-deficient conditions for three generations. The oral administration of DHA for 12 weeks to Amyloid beta-infused AD model rats significantly improved memory loss. The mechanism of the ameliorative effect was associated with: (i) increases in the levels of DHA and decreases in levels of arachidonic acid in both brain cortex and hippocampus, with resulting increases in the molar ratios of DHA/AA; (ii) decreases in the levels of LPOs in the cortex–hippocampus of DHA-fed AD model rats; (iii) decreases in reactive oxygen species (ROS) levels in synaptosomal plasma membranes; (iv) decreases in the levels of histone-associated DNA fragments, an apoptosis marker; (v) decreases in cortical lipid-raft cholesterol; (vi) increases in lipid-raft DHA levels and (vii) decreases in the amyloid burden in the cortex of AD model rats.[28]

Effect of DHA on lipid rafts

Lipid rafts or caveolae are specialized membrane structures consisting of saturated fatty acid- and cholesterol-rich membrane-invaginated floating microdomains. They harbor many key proteins and serve as signaling platforms to facilitate the transfer of substrates and protein–protein and protein–lipid interactions to facilitate specific signal transduction in living cells. Previous studies show that DHA pre-administration to rats inhibited hemolysis by Aβ1–42.[29] This activity was accompanied by increased DHA levels and membrane fluidity and by decreased cholesterol levels, lipid peroxidation, and reactive oxygen species in the RBCs of the DHA-pretreated rats, suggesting that the antioxidant activity of DHA rescues RBCs from oxidative damage by Aβ1–42.

Dietary supplements DHA and its effect on humans

Docosahexaenoic acid, or DHA, is a type of omega-3 fat. Like the omega-3 fat eicosapentaenoic acid (EPA), DHA is plentiful in oily fish, such as salmon and anchovies.

Our body can only make a small amount of DHA from other fatty acids, so you need to consume it directly from food or a supplement.

Reduces Heart Disease Risk

In one study in 154 obese adults, daily doses of 2,700 mg of DHA for 10 weeks increased the omega-3 index, a blood marker of omega-3 levels that's linked to a reduced risk of sudden heart-related death by 5.6%.The same daily dose of EPA increased the omega-3 index of the same participants by only 3.3%.[30]

DHA also decreased blood triglycerides more than EPA, 13.3% versus 11.9% and increased "good" HDL cholesterol by 7.6% compared to a slight decrease for EPA.[31]

Notably, DHA tends to increase "bad" LDL cholesterol levels but mainly the number of large, fluffy LDL particles, which unlike small, dense LDL particles aren't linked to increased heart disease risk.

May Improve ADHD

Attention deficit hyperactivity disorder (ADHD) characterized by impulsive behaviors and difficulty concentrating generally starts in childhood but often continues into adulthood

As the main omega-3 fat in your brain, DHA helps increase blood flow during mental tasks. Research has shown that children and adults with ADHD commonly have lower blood levels of DHA.

In a recent review, seven of nine studies that tested the effects of DHA supplements in children with ADHD showed some improvement such as with regard to attention or behavior.[32]

For example, in a large 16-week study in 362 children, those taking 600 mg of DHA daily had an 8% decrease in impulsive behaviors as rated by their parents which was twice the decrease observed in the placebo group.[33]

Fights Inflammation

Omega-3 fats such as DHA have anti-inflammatory effects. Increasing your DHA intake can help balance the excess of inflammatory omega-6 fats that is typical of Western diets rich in soybean and corn oil. DHA's anti-inflammatory properties may reduce your risk of chronic diseases that are common with age, such as heart and gum disease, and improve autoimmune conditions like rheumatoid arthritis, which causes joint pain.[34]

For example, in a 10-week study in 38 people with rheumatoid arthritis, 2,100 mg of DHA daily decreased the number of swollen joints by 28%, compared to a placebo. [35]

Flaxseed in diet and its effects on humans

Dietary flaxseed has an impressive and growing research literature supporting its use in a variety of health conditions. The main bioactive compounds in flaxseed include alpha-linolenic acid (ALA), lignans and fiber. Four common forms of flaxseed available for human consumption include whole flaxseed, ground flaxseed, flaxseed oil and partially defatted flaxseed meal.

Data suggest that omega-3 fatty acid, ALA, which is enriched in flaxseed, may have functional significance for the brain.

In a cross-sectional study, Djoussé et al. [36]found that a higher intake of dietary ALA (highest tertiles 0.89 g/day) was inversely associated with heart rate-adjusted QT and JT intervals in a dose-response manner in both men and women. The authors suggested that dietary ALA might be associated with a reduced risk of abnormally prolonged repolarization.

In a study of 30 healthy adults, ALA supplementation increased BDNF levels. BDNF is a vital growth factor for neurons; the authors of this study concluded that ALA is worth studying in the context of stroke recovery.[37]

In a study of 51 bipolar disorder patients, flaxseed oil supplementation helped improve their mood.[38]

Quantification of Docosahexaenoic acid

Fish oil products that have so much EPA and DHA contents, are available, and have very variable prices. The profiles of the chemical compounds are to be identified by using GC-MS chromatography method. The GC-MS method, used in fish oil analysis for the determination of EPA and DHA, has been confirmed to be effective and accurate.[39] Also, EPA and DHA are to be analyzed, by using High Performance Liquid Chromatography (HPLC), and Liquid Chromatography Mass Spectrometry (LC-MS), with the HPLC not as sensitive enough like the GC-MS, while requiring very high costs when using LCMS.[39]Also, clinical trials are to be conducted, in comparing the two products, to observe the effects of EPA and DHA, in the reduction of blood cholesterol levels (LDL, total cholesterol, and triglycerides).

Previous study done by Lorensia et al.[40] used the following conditions, Shimadzu QP-2010 SE brand GC-MS, Japan-using capillary column RTX-5SM (60 m x 0.25 mm, layer thickness 0.25 μm), with minimum column temperature of 330°C-350°C, used for sample separation. For temperature programming, the oven was maintained at 80°C for one min, increased at intervals of 10°C/min to 250°C, then reduced to 8°C/min to 280°C, and balanced for 5 min. Split injection was performed at a ratio of 1:200, as an helium carrier gas, with 1 μl injection volume of 0.73 ml/min was used. The mass spectrum, was operated in electron impact mode (EI). Furthermore, other parameters included, pressure 100 Kpa, injection temperature 250°C, ion source EI 200°C, interface temperature 220°C, electron energy 70 eV, delay solvent 5 min. For the qualitative analysis the full scan mode used for variously was 40-400m/z

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