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EXPLORING THE BIOLOGICALLY ACTIVE METABOLITES OF *ISOCHRYSIS GALBANA* IN PHARMACEUTICAL INTEREST: AN OVERVIEW

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ABSTRACT: Microalgae biomass has been recognized to have great potential as a source of novel bioactive compounds with industrial as well as health promoting applications in human, animal and aquatic lives. Microalgae have been gaining attention continuously due to its bioactive compounds. These bioactive compounds are primary and secondary metabolites produced by microalgae in order to adopt adverse environmental conditions. The simple growth requirement, higher mass productivity in short harvesting time making microalgae promising over other natural source of bioactive compounds. Several species of microalgae have undergone various screenings to identify and tap into these valuable resources, among them are the *Isochrysis galbana*, a brown microalgae belonging the class haptophyta. It is widely used as a feed for marine organism in aquaculture because of its high lipid content. Recently it is found *Isochrysis galbana* also exhibited the potential of being a source of high-value compounds with distinct biological activities including antitumor, antibacterial, antioxidant properties, anti-inflammatory and hypochloesteromic. These activities have a wide range of applications in various industries that have not been broadly explored and fully exploited. The aim of this review paper is to update previous researches on the biological activity of *Isochrysis galbana* and to explore it as a pharmaceutical agent.

INTRODUCTION: Nowadays, there is a huge interest among consumers and food industry on products that can promote good health, improve the state of wellbeing and decreases the risk of diseases [1, 2]. Over the last few decades many microalgae has attracted the interest of researchers due to its high nutritional value and vast variety of novel metabolites that can be used in bioremediation [3], biofuel [4], biofertilizer [5], human food [6], animal feed [6], and pharmaceutical industry [7].

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Extensive pharmaceutical and nutraceutical researches have being conducting globally for production of bioactive compounds from microalgae. Among these microalgae, *Isochrysis galbana* is one of the common marine microalgae used in mariculture to feed for bivalves & larva of fish, crustaceans, and mollusks [8]. Initially they have gained notice due to its high content of lipid that can be used in aquaculture and biofuel.

Recently, it has found *Isochrysis* also have balanced composition of several important bio-molecules, namely polysaccharides, fatty acid, carotenoids, vitamins, sterols which have the potential to improve the nutritional value of human foods, animal feed and have therapeutic potential against several diseases like cardiovascular disease cancer, diabetes, infectious diseases *etc*. [9, 10].

Nutraceutical and pharmaceutical scientists raised interest in *I. galbana* due to its simple growth requirement, ability to grow in extreme environmental condition, higher growth rate and productivity [11]. Isochrysis are golden brown marine photoautotrophic microalgae belonging to the class haptophyta that use light energy and inorganic nutrients (carbon dioxide, nitrogen, phosphorus, *etc*.) to develop and synthesize bio-compounds that have high aggregated nutritional and therapeutic values. The biochemical composition of microalgae is depends on growth phase and culture conditions. These are important factors that influence the metabolism of microorganisms, thus directing the synthesis of specific compounds of interest.

Therefore, culture conditions have to be optimized to maximize growth rate and production of valuable metabolites. *I. galbana* has been used as feed in aquaculture since long time [10, 12]. Although, limited studies found that explore its bioactive compounds and proves their therapeutic potential. This review aims to collate information from limited literature available on the great potential of biologically active metabolites of *Isochrysis galbana* for commercial uses. The aim of study is to review the main bioactive compounds in *I. galbana* and its therapeutic potential. Here we discuss few bioactive compounds- carotenoids, omega 3 fatty acid, sulfate polysaccharides and update previous researches on the biological activity of *Isochrysis galbana* to explore it as a pharmaceutical agent.

Valuable Bioactive Compounds: Bioactive compounds are heterogeneous group of essential and non-essential compounds commonly present in small concentrations in plants and food products. It haves the potential to provide health benefits beyond the basic nutritional value of the product [13]. Recently microalgae have received attention due to its novel and structurally diverse bioactive compounds. They have unique ability to survive in adverse environmental condition and in order to adapt new environmental surroundings, they biosynthesize and accumulates different primary and secondary bioactive compounds that have potential pharmaceutical and therapeutic values [14]. These therapeutically effective compounds usually accumulated in biomass or in some cases released extracellular into the medium [15]. Most of the valuable compounds produced by microalgae are secondary metabolites. These metabolites are nothing but organic compounds that do not accumulates or participate directly in growth or development, but appear under stress conditions [16]. Isochrysis characterized by fast growth rate, wide temperature and salinity tolerance and absence of toxins [11]. They contain many bioactive compounds, such as proteins, polysaccharides, lipids, carotenoids, vitamins, enzymes and other high-value compounds with pharmaceutical and nutritional importance that can be employed for commercial use [9]. This study reviews selected bioactive compounds-carotenoids, omega 3 FA, polysaccharides and its role in cardiovascular disease, neurodegenerative diseases and cancer.

Carotenoids: The main pigments of the *Isochrysis galbana* are the light harvesting pigments chlorophyll a, chlorophyll c, fucoxanthin and have diadinoxanthin in minor concentration [16, 17, 18]. Under light stress, diadinoxanthin can be converted into diatoxanthin that have higher ability to quenching of excessive light energy and protect it from light stress [19, 20, 21]. Fucoxanthin is a main carotenoid present in *Isochrysis galbana* exhibits potent antioxidant activities [22, 23]. After absorption in human body it is metabolized into fucoxanthinol, amarouciaxanthin A and halocynthiaxanthin [24]. Antioxidant activity (AO) of fucoxanthin is greater than other antioxidant compounds like beta carotene, alpha tocopherol and phenolic compounds.

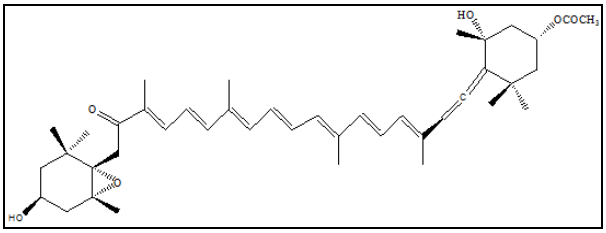

FIG. 1: STRUCTURE OF FUCOXANTHIN

It has reported fucoxanthin has a strong radical scavenging activity as compare to other carotenoids such as zeaxanthin, β-carotene and lutein [25]. This attributed to the unique molecular structure of fucoxanthin, which have double allenic bonds at C-7′ position with several conjugated double bond [26] as shown in **Fig. 1**. A number of studies have examined the metabolism, safety, and bioactivities of fucoxanthin, including its anti-cancer, anti-

obesity, antioxidant, anti-inflammatory, anti-diabetic, and anti-angiogenic activities [27, 28].

Omega 3 Polyunsaturated Fatty Acid: Based on the position of first double bond in carbon chain, there are two types of polyunsaturated fatty acid (PUFA)-omega 3 fatty acid (n-3FA) and omega6 fatty acid (n-6FA). Most common type of n-6 FA are Linoleic acid (LA; C18:2), Arachidonic acid (AA; C20:4) and n-3 FA are α-linolenic acid (ALA, 18:3), eicosapentaenoic (EPA; C20:5) and docosahexaenoic (DHA; C22:6) acids, structure were shown in **Fig. 2**. Both are essential fatty acids and are not synthesized by human due to the absence of enzyme required placing double bond at n-3 and n-6 position. LCPUFA especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) provide significant health benefits and needed to be supplied by diet.

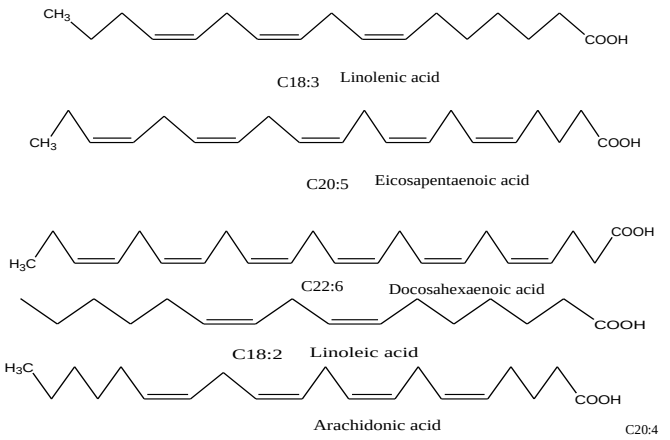

FIG. 2: STRUCTURE OF POLYUNSATURATED FATTY ACID

Currently, Marine fatty fish are the key source of n-3 fatty acid (n-3FA) in human [29]. However, its undesirable taste, typical smell, cultural constraint, decline resources, increasing risk of contamination and prices, has created the demand for an alternative sources. Microalgae are the primary producer of EPA and DHA that are eventually accumulated to higher animal through food chain [30]. Vegetable sources are rich in LA, ALA but poor in EPA and DHA.

In the metabolic pathway of ALA, it converted into EPA & DHA however; this conversion of ALA into EPA and DHA in human is very low due to the deficiency of desaturase enzymes. Therefore, there is need to direct intake of EPA & DHA rich dietary sources. Unlike human, in microalgae, n-3 and n-6 FA series are interconvertable as shown in **Fig. 3**.

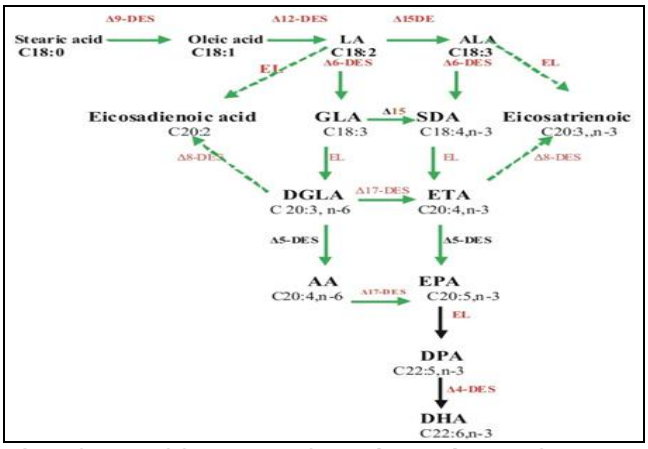

FIG. 3: BIOSYNTHETIC PATHWAY FOR THE POLYUNSATURATED FATTY ACID IN MICROALGAE

EL- elongase enzyme DES- desaturase enzyme LA-Linoleic acid, ALA-alpha linolenic acid, SDA- stearidonic acid, GLA- gamma linolenic acid, DGLA- dihomo-γ linolenic acid, ETA- eicosatetraenoic acid, AA-Arachidonic acid, EPA- eicosapentaenoic acid, DHA- docosapentaenoic acid, DHA- docosahexaenoic acid.

Isochrysis galbana is a marine microalga contain significant amount of LCPUFA in particular EPA and DHA. Although composition of lipid within cell differ with various culture conditions such as light intensity, culture medium composition, temperature. It has been acknowledged that n-3 FA particularly EPA & DHA play important role in many metabolic activities and have high therapeutic importance against cardiovascular disease (CVD), inflammatory disease, neuro-degenerative disease, cancer. There is currently a large demand for microalgae in the nutraceutical and pharmaceutical industry due to their sustainable productivity.

TABLE 1: COMPARISION OF FATTY ACID COMPOSITION (% OF TOTAL FATTY ACID) OF *I. GALBANA* WITH COMMON VEGETABLE OILS [31, 32]

Fatty acid	*I galbana*	Sunflower	Safflower	Sesame	Rice Bran	Rapeseed
14:0	19.0	0.09	0.1	-	0.39	-
16:0	9.1	6.2	6.7	9.7	20.0	4.6
18:0	0.7	2.8	2.4	6.5	2.1	1.7
16:1	nd	0.12	0.08	0.11	0.19	0.21
18:1	10.4	28.0	11.5	41.5	42.7	63.3
18:2	6.5	62.2	79.0	40.9	33.1	19.6
18:3	9.6	0.16	0.15	0.21	0.45	1.2
SFA	29.1	9.4	9.3	9.4	22.5	6.3
MUFA	10.4	28.3	11.6	28.3	44.0	72.8
PUFA	34.5	62.4	79.1	62.4	33.6	20.9
n-3	28.0	0.2	0.2	0.2	0.5	1.2
n-6	10.0	62.2	79.0	62.2	33.1	19.6

Table 1 illustrated comparison of fatty acid composition of *I. galbana* to the conventional vegetable oils and depicts that it could be possible dietary source of n-3FA in infant formula, animal feeds and human nutrition [30].

Polysaccharide: Polysaccharide (PS) is polymeric carbohydrate structures that are formed of monosaccharide *via* different glycosidic bond. The carbohydrate content of Isochrysis represents around 13% of dry matter. Mono-sugar compositions of Isochrysis consist of 2.07% fucose, 2.50% rhamnose, 2.72% arabinose, 8.49% xylose, 15.7% mannose, 32.73% galactose and 35.79% glucose. Sun first isolated intracellular and extracellular polysaccharides from *Isochrysis galbana*. **Fig. 4** elicited it is a highly branched chain of β-type hetero polysaccharide with (1→3) (1→6) glucan [33]. Glucan contains linear chain of (1 → 6)-linked β glucopyranose (GLc) consist backbone of the structure. Every residue is substituted at position 3 by Glc, which in turn may be substituted at C-6 by a single Glc or by rather short (up to tetrasaccharide) oligosaccharide chains. [34]. Polysaccharides have a wide array of biological activity like anticoagulant, immune-modulatory. These biological activities of polysaccharide depends on the ratio of 1 → 3 and 1 → 6 linkage (degree of branching) and chain length. Sun isolated three polysaccharides, IPSI-A, IPSI-B and IPSII from the *Isochrysis galbana* and demonstrated to have antioxidant activity [35]. They have wide range of biological activities and potential health benefits, making them interesting compounds for the application in therapeutics, and pharmaceuticals industry. It also has free radical scavenging ability and may reduce risk of chronic diseases like CVD, arthritis, cancer, neurodegenerative diseases. [37, 38, 39].

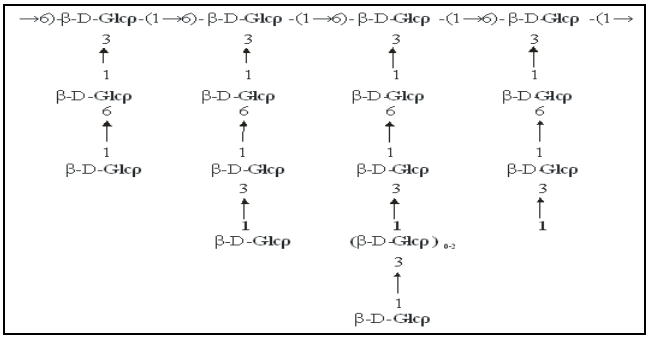

FIG. 4: HIGHLY BRANCHED STRUCTURE OF THE β-GLUCAN FROM *I. GALBANA* [34]

Biological Activity of *Isochrysis galbana:*

Cardioprotective Activity: Cardiovascular disease (CVD) is one of the leading causes of death worldwide [40]. CVD is a group of diseases that affect the heart, blood vessels and blood circulation include atherosclerosis, CHD, stroke, heart failure, thrombosis and peripheral arterial disease. Cardio protective activity of *I. galbana* is attributed to its antioxidant, anticoagulant and cholesterol lowering properties. It scavenges free radical, thereby prevent oxidation of low-density lipoproteins (LDL), which carry cholesterol into the blood stream, significant potential to cause atherosclerosis [41]. Nuno conducted an experiment on diabetic rat and found daily consumption of 50gm *Isochrysis galbana* for 8 weeks lower serum cholesterol and triglyceride accredited to its polysaccharide content [42]. Mechanisms involved in lowering cholesterol are not yet completely understood however; Oakenful proposed that it lowers serum cholesterol by increasing bile excretion and interfering with micelle formation and lipid absorption [43].

It may also possess anticoagulant property, although there are only few studies on anticoagulant properties of microalgae [44]. The most recognized mechanism is that PS inhibits clot formation due to its heparin like activity. Pereira suggested the anti-coagulated properties of sulfated polysaccharides depends on its sulfated content particularly distribution/position of sulfate groups and configuration of polymer chain rather than amount of sulfur residue [45]. *Isochrysis galbana* has been acknowledged due to its high n-3 LCPUFA. Its regular consumption may reduce the risk of cardiac arrhythmias, myocardial infarction, thrombosis, and cardiac arrest [46]. n-3 has anti-arrhythmatic activity based on the ability of EPA to incorporate into myocardial cell membranes [47]. Incorporation of EPA in the cell membrane potentially alters the eicosanoids production and ion channel function. It increases membrane fluidity in cardiac cells, thereby preventing atrial [48, 49]. Previous studies have demonstrated that EPA rich diet inhibits platelet aggregation, reduces blood viscosity, fibrinogen concentration, and increases plasmogen activator thus prevents CVD. However, further studies needed to explore the role of *Isochrysis galbana* in thrombosis, arrhythmia and other cardiac event.

Antitumor Activity: Cancer is a disease where cell continue to grow and divide. Multiple mechanism involve in cancer prevention includes, inhibition of excess cell growth, enhanced apoptosis, suppression of neoplastic transformation and antiangiogenicity. Free radical and progressive oxidative damage induces formation of cancer cell lines. Isochrysis have significant amount of antioxidant compound such as carotenoids (fucoxanthin), phenolic compounds, and α tocopherol. Beneficial effect of fucoxanthin in prevention of cancer is well established [50, 51]. Several study had reported valuable effects of fucoxanthin in prevention of different type of carcinomas includes prostate and lung [52], colon cancer [53], lung cancer [54, 55], urinary cancer, gastric cancer, breast cancer T cell leukemia [56]. Antitumor effect of fucoxanthin have been mediated through different mechanism includes apoptosis, arrest cell cycle, anti proliferation, anti angiogenesis [57]. Rodrigues and colleagues also found fucoxanthin was one of the strongest carotenoids only suppressed by astaxanthin for scavenging HOCl [58].

The antioxidant activity of algal fucoxanthin is higher than α tocopherol by effectively protecting from oxidative damage [59]. Antioxidant potential of *Isochrysis galbana* have been identified by Natrah et al may contribute in prevention of various type of cancer [32]. Usually antioxidant activities of carotenoids were assessed by DPPH, hydroxyl and Nitric oxide (NO) radical scavenging activity. Methanol extract of *Isochrysis galbana* have 34.18% DPPH radical scavenging properties, 67.35% hydroxyl radical scavenging properties, 37.33% NO scavenging properties [61]. Goiris *et al*., establish antioxidant activity of *Isochrysis galbana* is due to both carotenoid and phenolic content [62]. Although antioxidant activity of phenolic component of microalgae faltering. Li found no antioxidant activity of phenolic compound [63] whereas Jaime *et al.,* [64], Geetha *et al*., [66] Custódio *et al.,* [66] observed high antioxidant capacity of phenolic compound. This is further supported by Hajimahmoodi [67], Custodio *et al*., [68] demonstrated the antioxidant activity of microalgae is due to the presence of phenolic compounds.

Antitumor activity of *Isochrysis* species have been identified in many studies such as acetone extract of *I. galbana* T-ISO significantly reduced the viability of human hepatic carcinoma Hepatic G2 cell [68]. Crude polysaccharide of *Isochrysis galbana* has immune-stimulating ability by the induction of IL-1 within murine macrophage [69]. Sadovskaya *et al*., confirmed the anti-tumor potential of PS extract of *Isochrysis sp.* as they inhibit the proliferation of U937 human leukemic monocyte lymphoma cells [34]. Sun et al isolated intracellular polysaccharide IPS-I, IPSII, IPSIII from *Isochrysis galbana* posses significant antioxidant properties [33]. Anti oxidative property of PS attributed due to its ability to prevent accumulation and activity of free radical and other reactive species [38, 70].

Thereby, provide protection against oxidative and radical agent. Rocha de Souza [71] and Ye *et al.,* [72] found PS inhibits tumor cell proliferation in vitro and in mice. The exact mechanism of action is not known yet but it is suggested that it blocks the interaction of cancer cells with basement membrane and inhibit the adhesion of tumor cell to various substrate [73]. Role of n-3 fatty acids in prevention of cancers has not been fully established. It has found ratio of n3/n6 is a determining factor for the prevention of carcinogenesis [74, 75]. High n-6 and low n-3 FA produces inflammatory metabolites which increases proliferation of cells. *In vitro* studies found high AA induces pancreatic cancer whereas EPA suppresses [76].

Neuro- protective Activity: Marine algae found to be a potent neuro protective agent and could be introduced for the preparation of novel functional ingredients in pharmaceuticals for the treatment and or prevention of neurodegenerative disease [77]. Excess production of free radical and reactive oxygen species (ROS) is the fundamental mechanism underlying human neurological disorder [78]. Overproduction of free radical leads oxidative stress and causes cellular damage that leads many neurological disorders to brain cells.

It is well stabilized that metal also generate highly toxic free radicals, resulting in oxidative damage responsible for the development of neurological disorders [79]. Radical scavenging and metal chelating activity is a valuable approach in treatment neurodegenerative diseases [80, 81, 82]. *I. galbana* have significant radical scavenging ability and have high ability to chelate Fe^{2+} and Cu^{2+} [60].

Antioxidant present in *Isochrysis* like fucoxanthin, tocopherol, and phenolic compound may prevent or reverse the age-related changes in the central nervous system. They exhibit antioxidant activity by scavenging free radical and other reactive species such as reactive oxygen species (ROS) & reactive nitrogen species (RNS) and chelating catalytic metals [83]. Fucoxanthin is a major carotenoid of *Isochrysis galbana* (1.85% DW) known for its antioxidant properties and neuroprotective activities [84]. Other theory advocated that n-3 FA plays a significant role in proper development of nervous system, cognitive development and memory related learning. It modulates electric signal transduction mechanism by affecting ion channel function and receptor system.

Composition of fatty acid in brain cell membrane increases neuro plasticity of nerve membrane, increases synaptic transmission**,** regulates production and transmission of neurotransmitters such as serotonin and dopamine [85, 86]. DHA is the major fatty acid of brain consists of 12-16% of total fatty acid in grey matters. It has been found in clinical trials that learning capacity and visual acuity increases with DHA [87]. Several studies documented the positive effect of DHA in neurological disorder [88, 89, 90, 91].

Most possible mechanism is the ability of DHA to incorporate in brain cell membrane and thereby, increase membrane fluidity and ability to bind ligand which initiates transduction process [92, 93, 94]. Antalis *et al.,* found in their study that low blood DHA/EPA may lead behavioral disorders including attention-deficit⁄ hyperactivity disorder (ADHD) [95].

Previous researchers found that high consumption of DHA lowers the incidence of age-related cognitive decline, dementia, risk of Alzheimer's disease (AD) and epilepsy. Role of PS extract of *Isochrysis* in neurological disorder have not been reported. Although sulfated polysaccharide from the other brown algae exhibit neuroprotective effect by decreasing apoptosis in neuronal cells and acetyl cholinesterase (AChE) inhibitory activity [96]. Recently found PS have appreciable antioxidant capacity involves metals chelating and free radical scavenging properties. This further supports the neuro-protective activity of polysaccharides [97, 98].

Antimicrobial Activity: Antimicrobial potential of microalgae has been recognized a long time ago. Microalgae extracts or their secondary products have inhibitory activity against many pathogens and cultured organism [99, 100, 101, 102]. Several compounds includes phenols, fatty acid, volatile halogenated hydrocarbons indoles, terpenes play important role in antimicrobial activity of microalgae. Antimicrobial activity of Isochrysis is attributed to its fatty acid content which vary with its different strain and cultural condition [103]. *Isochrysis galbana* produces and accumulates high content of lipid in stationary phase, when cells are not dividing. They release free fatty acid from lipid through enzymatic activity and discharge in media in late growth phase as a defensive mechanism against pathogenic bacteria, virus and other coexisting algae [101, 104]. These fatty acid and their derivates have antibacterial activity against a wide range of gram negative and gram positive bacteria [105]. Antibacterial activity of fatty acid may be due to its ability to bring bacterial cell lyses [106, 107, 108].

Duff noticed the ability of *Isochrysis galbana* to inhibit the growth of human pathogens such as *Streptococcus aureus* and *Streptococcus faecalis*, *proteus vulgaris* [100]. Srinivasakumar & Rajashekhar also found substantial activity of *Isochrysis galbana* against bacterial pathogens such as *E. coli Klebsiella pseudomoniae, Salmonella typii*, however, not noticed any inhibitory activity against vibrio strains [110]. Recently, Ceres *et al.,* found *Isochrysis galbana* produces toxic substance that reduce the count of vibrio strains like *Vibrio alginolyticus, Vibrio campbellii,* and *Vibrio harvey* to the undetectable level within week [111]. Beside fatty acid, chlorophyll a derivates such as pheophytin a and chlorophyllide found to have antibacterial activity [112].

Polysaccharides from brown algae (Phaeophyceae) contain some antiviral properties[113]. It have been found to reduce the growth of enveloped viruses including members of the flavivirus, togavirus, arenavirus, rhabdovirus, orthopoxvirus, herpes virus families and HIV virus too. Endocellular extracts of *Isochrysis galbana* have growth inhibiting properties against virus *rhabdovirus* of viral haemorrhagic septicaemia (VHSV) [108]. Many microalgae releases toxic secondary metabolites inhibit the growth of either their own species or

other coexisting microalgae or both [113]. Yingying *i*solated growth inhibitor $C_{22}H_{38}O_7$ from death phage of *Isochrysis galbana* has inhibitory effect against the growth of other coexisting microalgae like *Dunaliella salina, Platymonas elliptica, Chaetoceros muelleri and Phaeodactylum tricornutum* [114].

TABLE 2: IDENTIFIED BIOLOGICAL ACTIVITY OF *ISOCHRYSIS GALBANA*

Component	Result	Inference	Reference
Isochrysis galbana in rat	Lowers blood glucose from 132.5mg/dl to 83.8mg/dl	Hypoglycemic potential	42
Isochrysis galbana in rat	Lowers blood lipid from 66mg/dl to 54mg/dl	Hypolipidemic potential	42
Hexane extract of Isochrysis	High DPPH, Hydroxyl, NO scavenging activity	Antioxidant activity	32
Methane extract of Isochrysis	High DPPH, Hydroxyl, NO scavenging activity	Antioxidant activity	61
Polysaccharide extract of Isochrysis	Inhibit of proliferation of U937 human leukemic monocyte lymphoma cell	Potential anti-tumour activity	34
Acetone extract of Isochrysis	Lower the viability of human carcinoma Hep G-2 cells	Anticancerous potential	68
Acetone extract of Isochrysis	Increase the ability of chelate Fe^{2+}, have ability to inhibit AChE	Neuroprotective potential	68
Axenic Isochrysis culture	Effective to inhibit the growth of vibrio sp.	Antibacterial activity	110
Extract of *Isochrysis galbana*	Good antibacterial activity against pathogens *Klebisella pneumoniae, Proteus vulgaris, E. coli, Streptococcus aureus, Streptococcus facelis, Salmonella typhii*	Antibacterial activity	110, 115, 116
Cell free filtrate of *Isochrysis galbana*	Inhibit the growth of many coexisting microalga	Antialgal activity	114

Polysaccharides from brown algae (Phaeophyceae) contain some antiviral properties [113]. It have been found to reduce the growth of enveloped viruses including members of the flavivirus, togavirus, arenavirus, rhabdovirus, orthopoxvirus, herpes virus families and HIV virus too. Endocellular extracts of *Isochrysis galbana* have growth inhibiting properties against virus rhabdovirus of viral haemorrhagic septicaemia (VHSV) [108]. Many microalgae releases toxic secondary metabolites inhibit the growth of either their own species or other coexisting microalgae or both [113]. Yingying *i*solated growth inhibitor $C_{22}H_{38}O_7$ from death phage of *Isochrysis galbana* has inhibitory effect against the growth of other coexisting microalgae like *Dunaliella salina, Platymonas elliptica, Chaetoceros muelleri* and *Phaeodactylum tricornutum* [114].

Human Nutrition: Microalgae have been used for food for thousands of years [117]. However, the commercial cultivation was started in the early 1960's in Japan with the culture of Chlorella [118, 119, 120]. Microalgae for human nutritional requirements are currently being merchandized in different forms such as tablets, capsules, pastilles, liquids and nutritional supplements and are also incorporated into snacks, pastas, candy bars or chewing gum and in beverages [121, 122]. *I. galbana* has been used in aquaculture as animal feeds for century. Recently found it has high nutritional value with wide varieties of biologically active compounds. Nutritional composition of *I. galbana* studied by different researcher were shown in **Table 3**.

TABLE 3: NUTRITIONAL COMPOSITION OF *I. GALBANA*

Protein(%)	Carbohydrates(%)	Lipid(%)	References
40	26.8	14.5	Natrah *et al*., [32]
27.1	34.32	10.54	Gorgonio *et al*., [125]
29	12.9	23	Brown [128]
39.6	18	23.9	Fradigue *et al*.,[130]
38-40	8-17	18-24	Batista *et al*., [131]
39.6	23.9	18	Guzman and Ascencio [132]

It has good amount of protein, soluble, insoluble carbohydrates and significant percentage of polyunsaturated fatty acid, which varies with growth phase and culture conditions. Under optimum condition, it contains 12% to 50.8% protein, 21.7% to 21.9% lipids, and 7.6% to 14.2% carbohydrates [123, 124]. *I. galbana* attracted the interest due to its high PUFA content.

The most common source of PUFA is fish and fish oil, although accumulated toxins, smell, poor oxidative stability limits its application in food additive. Declined fish resources, generates algal oil demands in market. *Isochrysis galbana* present the highest output of EPA (4.8% on dry basis) using vertical plate glass reactor [126] and have potential to use as source of n-3 FA in both nutraceuticals and animal feed industries.

Carbohydrate in microalgae is in form of starch, sugar and other polysaccharides. The carbohydrate content of Isochrysis comprises about 13% of dry matter and contains both soluble and insoluble carbohydrates with good digestibility [127]. It has been seen that its nutritional composition are comparable to the common vegetable food commodities **Table 4** [125] and they can be used in the diet of humans and animals as natural foods with health benefits The high protein content and its amino acid pattern makes them non conventional protein source. **Table 4** elicited, the most abundant amino acids in isochrysis were glutamic acid and aspartic acid, whereas cysteine, methionine, tryptophan, and histidine were found in lower amounts (0.4% to 3.2%), and other amino acids were found in amounts between 3.2% to 13.5% [128]. Thus, their composition gives microalgae interesting qualities, which can be applied in human and animal nutrition. In addition, it contains biologically active compounds and possesses considerable antioxidant properties that could be applied in functional food and pharmaceutical industry [60]. However, prior to incorporation in food, drug and commercialization, algal material must be analyzed for the digestibility and presence of toxic compounds to prove their harmlessness. It have been found that its total digestibility is extremely high, which explains why there are no limitations to its use in foods and feeds [127, 129].

In addition several toxicological assessments have not revealed any toxic impacts or abnormalities in experiments with test animals [130]. Fradique *et al*., enhanced the nutritional value particularly EPA and DHA content of traditional pasta by incorporating *I. galbana* [131]. Nuno *et al*., conducted a study on diabetic rat and found consumption of the microalga *I. galbana* promotes body weight loss in healthy animals and helped to maintain weight in diabetic animals and it lowers glucose and cholesterol values and raises lactic acid bacteria counts too [42].

TABLE 4: NUTRITIONAL COMPOSITION OF CONVENTIONAL FOOD WITH *I. GALBANA* [32, 133]

Composition	*I. galbana*	Milk	Soyabean	Egg	Fish	Meat
Protein (%)	*47.9*	26	37	49	55	43
Carbohydrates (%)	*14.5*	38	30	3	1	1
Lipid(%)	*26.8*	28	20	45	38	34
Amino acid (g/100g dry weight)						
Histidine	2.5	3.3	2.6	2.4	1.45	3.2
Arginine	8.7	3.3	7.4	6.2	3.82	6.6
Valine	6.0	5.7	5.3	7.2	2.77	5.3
Lysine	12.1	7.8	6.4	5.3	4.72	8.2
Isoleucine	4.9	4.3	5.3	6.6	2.66	5.1
leucine	10.5	9.2	7.7	8.8	4.48	7.8
Threonine	6.1	4.5	4.0	5.0	2.31	4.5
Phenylalanine	6.1	5.6	5.0	5.8	4.35	4.2
Methionine	1.42	1.3	1.3	3.2	2.31	2.4
Tryptophan	1.53	1.4	1.4	1.7	0.57	-

CONCLUSION: In conclusion *Isochrysis galbana* has high nutritional value with considerable amount of biologically active compounds like n-3 fatty acid, fucoxanthin, polysaccharides that have a potential to utilize in various industries includes aquaculture, pharmaceuticals and human nutrition. Initially, they got attention as aquaculture feed, however present review find *I. galbana* can be alternative source of therapeutic and biological compounds such as essential amino acids, polysaccharides, monounsaturated and poly-unsaturated fatty acids, and fucoxanthin. They have a potential to incorporate in various traditional food such as bakery, pasta, dairy and confectionary products without much intervention in sensory quality. Thus, it can be use for food enrichment,

nutritional supplements, and powered formulation and as tablet and capsule, which will help in reducing all health problems of human beings. Although, vast experimental analysis and well structural clinical trial needed to prove the role of different bioactive compounds of *Isochrysis galbana* in prevention of human diseases and also constant efforts in research and development in the field of marine research is needed.

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