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Review Article

# MANIFESTATION OF METABOLIC SYNDROME BY TURBINARIA SPECIES: A REVIEW

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**ABSTRACT**

Metabolic disorder refers to a cluster of metabolic abnormalities (i.e., insulin resistance, hypertension, dyslipidemia, obesity, high cholesterol and high blood pressure). The metabolic disorder is fast becoming a global emergency. Drugs presently available in the market help in curing the disorder only up to some extent and providing symptomatic relief, in lieu of an array of side effects, hence it is the need of the hour to look for alternative strategy for prevention and treatment of metabolic syndrome. Marine natural products are a source of antihypertensive, antihyperglycemic, antioxidative, and anticancer agents possibly useful in the treatment or in the prevention of metabolic disorders. Through this review we have made an effort to throw some light on potential uses of the marine sea weed, a genus of brown algae Turbinaria (Phaeophyceae) as a potential agent for the treatment and amelioration of metabolic syndrome and related disorder, we have briefed about various chemical constituents found in the different species of Turbinaria and the role they can play in achieving the above said goal.

**Key words:** International diabetic federation – IDF, Metabolic syndrome – Met S

## INTRODUCTION

Marine organisms since a long time are being explored for a vast number of biological activity, they are known to be a very good source for a number of biologically active compounds having anti lipidemic, anti diabetic, hypocholesterolemic and cardioprotective activities. Present researchers still believe there is an ocean of medicinally active components which have not been explored to their full potential. One such marine resource are brown algae a sea weed which are widely known for being nutritionally active, but there is a plethora of unexplored jewel from this marine resource which can be used for the manifestation of a number of chronic conditions like obesity, diabetes, hypertension, hypercholesterolemia which are jointly known as metabolic syndrome.

Metabolic syndrome is a collection of conditions namely increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels that occur together[1], increasing the risk for heart disease, stroke and diabetes.

Metabolic syndrome is defined by a number of medical, biochemical, and metabolic factors that surges the risk of cardiovascular disease, diabetes mellitus[2]. By metabolic syndrome we mean presence of one or more of the following clinical symptoms namely type 2 diabetes mellitus[3,4], Insulin resistance, visceral adiposity, atherogenic dyslipidaemia, elevated blood pressure, and chronic stress[5].

Globally incidence of MetS ranges from less than 10% to 84%, according to the IDF approximations[6] one fourth of the world's adult population has the MetS[7] Higher standard of living, inactive lifestyle[8] and high body mass index (BMI) were ominously associated with MetS.

WHO has laid down a set of diagnostic criteria for the clinical identification of metabolic syndrome[9] i.e., for men a waist-to-hip ratio >0.90 for women waist-to-hip ratio >0.85 and/or BMI > 30 kg/m2 Lipids profile include TGs ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women and Blood pressure ≥140/90 mm H[10,11]. Appropriate prophylactic methodologies include lifestyle modification, majorly weight loss, inculcating healthy balanced diet, and routine work out[12]. Apart from these clinical manifestations there involves another approach which is, appropriate use of medicinal agents to reduce the specific risk factors such as Obesity, Type II Diabetes Mellitus and in appropriate lipid profile. Clinical management should be taken into consideration only when lifestyle modification stands unfruitful[13].

### Link between Metabolic syndrome and obesity

Metabolic syndrome is meticulously linked to overweight or obesity, it is because obese individuals are more prone to developing cardiovascular disease, type 2 diabete, incresed cholesterol levels hypertension and other relatef disorders which are the major clinical factors of metabolic syndrome, therefor treatment or manifestation of obesity should be considered as a prime approach to treat metabolic syndrome.

Obesity is a metabolic disorder implicated by excess body fat accumulation, raised body Mass Index (BMI) of more than 30 kg/m2 and increased waist circumference[14]. The disease is mainly due to excess and unhealthy food intake, poor physical

activity and genetic factors[15] Worldwide obesity in men and women is predicted to exceed 6% and 9% respectively.

**Need to look out for Alternative treatment strategy involving brown sea weed- Turbinaria *sp***

Commercially available anti-obesity drugs are limited in number, with lots of side effects, apart from these drugs few are in pre-clinical and clinical trials as well[16,17]. Presently there are four drugs which are approved by the Food and Drug Administration (FDA) for long term management of obesity namely Phenetramine, Naltrexone / Buprapion, orlistat, locaserin[18,19]. The only anti-obesity drug currently available in the market is orlistat, It is a pancreatic lipase inhibitor. Other agents are still under different stages of clinical trial[20,21]. These drugs primary drawback include their Side effects which were as grave as cardiovascular events and strokes, as was in the case of Sibutramine due to which they were withdrawn from the market or banned. This poses a dire need to look for new anti-obesity agents, especially from biological sources [22].

Marine algae, chiefly seaweeds are a potential source of a number of medicinally active compund, including anti-obesity agent[23]. Seaweed is multicellular, marine algae which can grow to up to 60 metres in length. Seaweeds include members of the red, brown and green algae[24, 25]. They belong to kingdom Protista meaning they are not Plants. Like plants they use the pigment chlorophyll for photosynthesis apart from that they also contain other pigments which may be coloured red, blue, brown or gold[26].

They are divided into three groups:
Brown Algae (Phaeophyta)
Green Algae (Chlorophyta)
Red Algae (Rhodophyta)

Seaweeds are a nourishment source for marine organisms such as sea urchins and fishes. The kelps form dense wilds which support most of the underwater communities offering both food and shelter.

Brown algae are the most prevalent type of algae. There are between 1,500 and 2,000 species of Brown Algae.

They comprise of an extra pigment (fucoxanthin), which often masks the green chlorophyll shared by all algae. Their colour ranges from an olive green to various shades of brown[27].

Brown algae grow in a wide range of sizes and forms. The smallest members of the group grow as tiny, feathery tufts of threadlike cells no more than a few centimetres long. Kelps grow in size ranging from the two-foot-tall sea palm Postelsia to the giant kelp Macrocystis pyrifera, the largest of all the algae[28].

The cell wall of brown algae comprises of a bi layer the inner layer provides strength and is composed of cellulose; the outer wall layer is algin, a jelly-like material when wet but it becomes hard and brittle when it dries out. Compounds made from algin are used as thickening, stabilizing, emulsifying, or suspending agents in industrial, pharmaceutical, and in foods.

One of these potential brown algae belongs to the genus Turbinaria. It is a genus of brown algae (Phaeophyceae) found mainly in tropical marine waters. It generally grows on rocky substrates [31]. Over 33 species of this genus have been known so far.

These brown algae are well known for their extensive pharmacological activities ranging from anti-oxidant, anti-diabetic, anti-obesity, to anti-proliferative, anti-cancer, anti-fungal etc., as they have a vivid chemical composition.

This was confirmed by several studies such as one done by Paramsivam Deepak et al, in turbinaria ornata he reported the presence of saponin, alkaloids, amino acids, fixed oil and fat. Spectral data confirmed the presence of functional groups such as alcohols, amides, aromatics, amines, alkyl halides, alkynes, alkanes and carboxylic acids. Using GC-MS spectral method the presence of 13 active compounds were revealed. Few of the major constituents can be named as follwed 1,2-benzenedicarboxylic acid, butyl 2-methylpropyl ester (MW: 278, MF: C16H22O4, RT0.941), n-hexadecanoic acid heptatriactontadien-2-one, 1,2-benzenedicarboxylic acid, mono(2-ethylhexyl) ester cholest-5-En-3-ol, 24-propylidene[29].

Apart from the above constituents Turbinaria species also contain phenolic compounds. The total phenolic contents of brown seaweeds belonging to Turbinaria spp. [Turbinaria *conoides* (*T. conoides*) and Turbinaria *ornata* (*T. ornata*) was evaluated by Kajal et al. Folin-Ciocalteu method was used to determine the total phenolic content of the extracts. The Ethyl acetate (EtOAc) fraction of *T. conoides* registered significantly higher phenolic content (105.97 mg GE/g) than that of *T. ornata* (69.63 mg GE/g. In the same study anti-oxidant activity of the extracts were determined by DPPH radical scavenging activity, ethyl acetate extracts from T. ornata showed promising anti-oxidant activity30. Since reactive oxygen species (ROS) play a key role in initiating and promoting several diseases such as cancer cardiovascular events, obesity Turbinaria species which are rich in antioxidants can become probable lead for the management of metabolic syndrome.

Bio prospecting of Turbinaria Macro algae as a Potential Source of Health Protective Compounds was Reported by Milena et al which aimed to characterize this Turbinaria macroalgae species, the biological activity such as anti-proliferation and antioxidant capacity were assessed by using *in vitro* cell-based tests, a number of biochemical assays like DPPH method were used for establishing anti-oxidant activity of algal extracts. High potential U-HPLC/HR-MS/MS instrumentation were used for screening of compounds and understanding the chemistry of the possible responsible compounds for bioactivity but this study was unable to unambiguously determine and isolate the compounds responsible for this bioactivity[31].

As discussed earlier diabetes is one of the clinical factors of metabolic syndrome. In a study by Unnikrishnan et al, crude extracts of marine seaweed, Turbinaria *ornata*, were tested for their ant diabetic potential using enzyme inhibitory assays ($\alpha$-amylase, $\alpha$-glucosidase, and dipeptidyl peptidase-IV). Among the tested extracts, methanol and acetone extracts showed significant inhibitory effects on $\alpha$-amylase. The GC-MS analysis of lead extracts showed the presence of major compounds, hentriacontane, z, z-6, 28-heptatriactontadien-2-one, 8-heptadecene, and 1-heptacosanol. Such findings indicate that Turbinaria *ornata* could be used as a potential source for further *in vivo* studies in controlling hyperglycemia[32].

Plethora of studies has shortlisted three major bioactive compounds from brown seaweeds which have the potential as anti-obesity anti cholestrolemic agents namely fucosterols, fucoxanthin, fucoidans [33].

**Fucosterols from turbinaria species**

Phytosterols / stanols are natural Hypocholesterolemic compounds which have the ability to lower blood LDL-cholesterol levels and hence atherosclerotic risk. But they do not influence the serum levels of HDL-cholesterol, known to be favourable for preventing disease. They are not detrimental as the mechanism of action is due to the inhibition of cholesterol absorption across the intestine. Plant sterols/stanols not only act synergistically to the statins, the most widespread cholesterol-lowering agents that inhibit hepatic cholesterol synthesis, but is found to be as effective as statins. Fucosterols are phytosterols found in brown sea weeds known for their plethora of biological activities like cholesterol lowering, anti-oxidant, anti-diabetic properties. Presence of Fucosterols has been reported in a number of turbinaria species. Sheu et al has isolated 9 different fucosterols from the brown algae Turbinaria connoides. Some of these fucosterols were designated as 24-ethylcholesta-4,24(28)-diene 3-one [34].

S.Sadish Kumar et al has isolated two new steroids 3,6,17-trihydroxy-stigmasta-4,7,24(28)-triene (**1**) and 14,15,18,20-diepoxyturbinarin (**3**), together with a known compound, fucosterol (**2**), from the cyclohexane extract of *Turbinaria conoides*. The structures were elucidated on the basis of spectroscopic evidence[35].

Jung et al reported a study on fucosterol obtained from Ecklonia stolonifera and suggested, it could be used as a potential anti obesity agent based on the fact that fucosterol inhibited adipocyte differentiation and lipid formation. According to the study methanolic extract of Ecklonia stolonifera showed considerably anti adipogenic activity. Fucosterol lessened lipid contents in a concentration-dependent manner without showing any cytotoxicity. It was found that Fucosterol treatment effected the expression of several adipocyte marker proteins such as peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT/enhancer-binding protein α (C/EBPα) by decreasing their levels[36].

Studies by Min Hien et al suggested that fucosterol can enhance plasma high-density lipoprotein concentrations, fucosterol induces the transcriptional activation of ABCA1, ABCG1, and ApoE, which are the key genes in reverse cholesterol transport, and thereby predominantly increases the efflux of cholesterol. It was also found that fucosterol did not induce cellular triglyceride accumulation in HepG2 cells, primarily because of its upregulation of a gene Insig-2a, which delays nuclear translocation of SREBP-1c, a key hepatic lipogenic transcription factor. From this it can be understood that fucosterol is a dual-LXR agonist that regulates the expression of key genes in cholesterol homeostasis in multiple cell lines without inducing hepatic triglyceride accumulation[37].

The potential of fucosterol as a lead in the Management of metabolic syndrome and its clinical factors is yet to be ventured in detail. The above studies indicate Turbinaria species to be a good source for various types of fucosterols which could be used for the manifestation of metabolic syndrome.

Though a number studies are being taken up on algal material to obtain potent bioactive molecules out of which few sure have the potential to emerge as an anti obesity agent but there is still a long way to go in terms of biological studies and study on human subjects.

**Fucoxanthins from Turbinaria Species**

A marine carotenoid named fucoxanthin in found in brown seaweeds, out of the total naturally occurring carotenoids fucoxanthin makes up to 10 percent[38,39]. It is found profusely in edible seaweeds such as Undaria pinnatifida, Laminaria digitata Hijikia fusiformis, and Turbinaria.

Fucoxanthin was reported in the brown seaweeds *Turbinaria turbinate* by Irwandi jaswir et al, *and was isolated and analysed by* Reversed phase-high performance liquid chromatography (RP-HPLC). The fucoxanthin contents of *T. turbinata* was found to be $0.59 \pm 0.08$ mg/gm dry-weight. Ultraviolet spectrum of fucoxanthin showed the maximum absorbance at 450 nm[40].

A Bio assay guided fractionation of a turbinaria ornata had a number of fractions showing potential antioxidant activity upon purification, spectral analysis using 1H and 13C NMR and ESI-MS ([M + Na]+ indicated the presence of a carotenoid which later was confirmed to be Fucoxanthin[41].

Fucoxanthin works on the mechanism of decreasing lipid metabolism via enhancing β-oxidation and reducing lipogenesis these studies were confirmed on obese mouse models[42], apart from that it also increases the activity of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) in epididymal adipose tissue which are known to be the key enzyme in lipid metabolism[43].

**Fucoidans from Turbinaria species**

Fucoidans are exceedingly sulfated polysaccharides, consisting of fucose, found mainly in the extracellular matrix of brown seaweeds. Fucoidans contain a wide number sugars namely D-xylose, D-mannose, D-galactose, L-rhamnose, arabinose, glucose, D-glucoronic acid.

Ellya sinurat et al has reported to have isolated 2.6% fucoidans from Tubinaria sp. Anti-lipidemic activity has been reported in Fucoidans extracted from *Undaria pinnatifida* these fucoidans were found to affect the mRNA gene expression of key adipogenic markers and expression of inflammation-related genes in adipocyte cells during adipogenesis[40,44].

*in vivo* bioactivity investigation by Ho Duc Cuong et al revealed that the fucoidan in the dose of 100 mg/kgP/day by oral administration aided in reducing cholesterol, triglyceride and LDL-cholesterol levels on obese mice.

Thuy Thi Thu Thanh et al have isolated a fucoidan from the brown seaweed Turbinaria ornata which contained high sulfate content and had very simple monosaccharide composition containing mainly fucose and galactose with ratio was classified as galactofucan.

Fucoidans show their activity by effecting key hormones like Hormone sensitive lipase as was shown in differentiated 3T3-L1 adipocytes. In another study, Kim et al. (2009) also demonstrated that fucoidans inhibited adipogenesis by suppressing the expression of acetyl CoA carboxylase (ACC) and peroxisome PPARγ[45].

**CONCLUSION**

Till date Marine algae, and constituents of marine algae have remained vastly unexplored. Though awareness regarding it has increased but talking on a commercial scale, there is still an ocean to explore. Our study briefs the major constituents from

them and their effect on management of metabolic syndrome but still a lot of work remains particularly understanding their effect on various animal models and understanding the molecular mechanisms remain the key, also there is still a need for more human trials of longer duration to understand the efficacy of such compounds.

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