Green remedy for hypertension from ICAR-CMFRI

Seaweeds are fast growing and potentially renewable resources that are currently being explored as novel and sustainable sources of compounds for both pharmaceutical and nutraceutical applications. One of the predominant oceanic flora, these invaluable marine herbs are considered as a prolific source of bioactive compounds as they are able to produce a great variety of secondary metabolites characterized by a broad spectrum of extraordinary medicinal properties. Lately the use of seaweeds for the development of new products as well as a source for obtaining high-added value compounds has attracted the food and pharmaceutical industries. ICAR-Central Marine Fisheries Research Institute (CMFRI), Kochi devoted its research programme for the development of promising bioactive molecules for human health and medication from seaweeds.

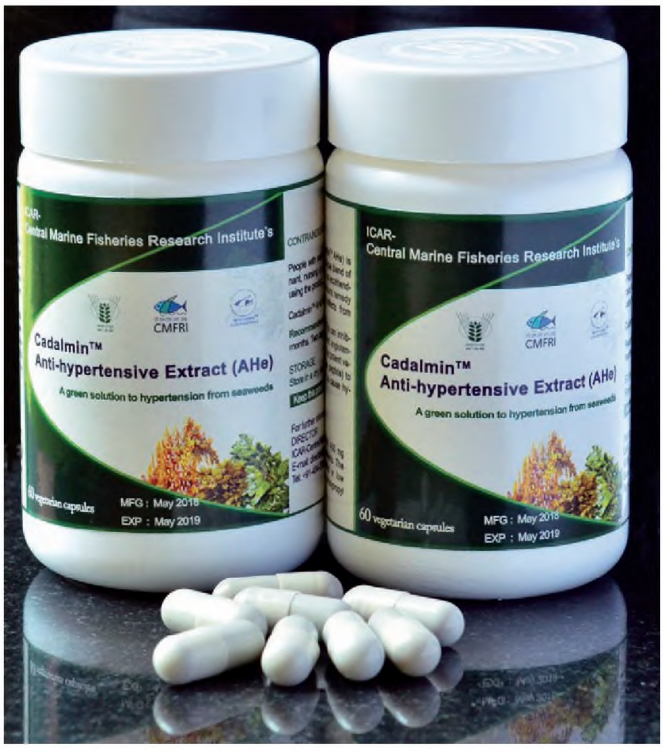
Bioactive pharmacophore leads from seaweeds were used to develop Cadalmin™AHe, which can be administered to regulate clinical indicators leading to pathophysiology that results in hypertension. Hypertension is one of the risk factors for strokes, heart

Sea weed

attacks, heart failure, and arterial aneurysm, and is a leading cause of chronic kidney failure. A search for safer and effective alternatives to synthetic drugs to combat hypertension led scientists to investigate into seaweeds, for valuable secondary metabolites, which are anti-hypertensive in nature, and could offer relief from hypertension.

Cardiovascular disease is termed as the leading cause of debility and premature death globally and hypertension as the most prevalent trigger for cardiovascular diseases. Angiotensin-I-converting enzyme (ACE-I) in the rennin angiotensin aldosterone system displayed an important part in the modulation of high blood pressure and cardiovascular function. It converts the inactive doctapeptide angiotensin-I (Ag-I) into the potent vasoconstricting octapeptide angiotensin-II (Ag-II), which potentially narrows the opening of a blood vessel lumen and increases vascular resistance. Synthetic drugs are used to manage blood pressure levels in hypertensive patients. The continuous use of the synthetic drugs is often associated with undesirable side effects, such as liver toxicity and adverse gastrointestinal symptoms. Therefore, the search for food-based or naturally derived anti-hypertensive inhibitors are of immense appeal and functional food products could likely perform the necessity. Dietary ingestion of seaweeds has been shown to decrease hypertensive complications in humans and also has strong antioxidant properties.

Cadalmin™AHe contains 100% natural marine bioactive ingredients from selected seaweeds. The active principles of this product effectively inhibit various mediators, which are responsible to cause hypertension through various metabolic pathways. Cadalmin™AHe blocks angiotensin converting enzyme that converts angiotensin I to angiotensin II. Decreased production of angiotensin II enhances natriuresis, lowers blood pressure, and prevents remodeling of smooth muscle and cardiac myocytes. The bioactive ingredients in the nutraceutical product effectively modulate the serum level of oxidative stress marker nitric oxide, lipid peroxidase and the potent vasoconstrictor angiotensin-II. Additionally, the formulation increases the serum level of vitamin E. Angiotensin II also has a direct vasoconstrictive effect, which increases blood pressure, and promotes inflammation and remodeling of cardiovascular system, leading to thrombosis or ventricular hypertrophy. The product regulates increased nitric oxide level in endothelial cells and maintains the normal vasodilation of the pulmonary arterial hypertension.



Animal model anti-hypertension experiments showed that active principles effectively decreased the angiotensin-II levels in the cadmium chloride ($CdCl_2$) induced hypertension in rats. Serum nitric oxide, lipid peroxidase and angiotensin-II levels were significantly decreased in hypertension affected group treated by Cadalmin™AHe. In $CdCl_2$ plus Cadalmin™AHe group serum NO level has been significantly regulated upto 8.5 µg/dL at 100 mg/kg body weight and 9.00 µg/dL at 200 mg/kg body weight compared to diseased group (13.06 µg/dL at 100 and 200 mg/kg body weight) and positive control group (9.17 µg/dL at 100 and 200 mg/kg body weight). The serum lipid peroxidase level in $CdCl_2$+ Cadalmin™AHe group was comparatively lesser 181.95 µg/dL at 100 mg/kg body weight and 179.58 µg/dL at 200 mg/kg body weight than diseased group (307.45 µg/dL at 100 and 200 mg/kg body weight) and positive control group (186.08 µg/dL at 100 and 200 mg/kg body weight). The serum angiotensin-II level in $CdCl_2$ + Cadalmin™AHe group were comparatively lesser 0.205 pg/mL at 200 mg/kg body weight than the diseased group (0.432 pg/mL at 200 mg/kg body weight) and positive control (0.211 pg/mL at 200 mg/kg body weight). Additionally, the serum vitamin E level were comparatively greater (0.23 µM/mg at 100 and 200 mg/kg body weight) than the diseased group (0.08 µM/mg at 100 and 200 mg/kg body weight) but comparable with the positive control group (0.20 µM/mg at 100 and 200 mg/kg body weight).

This vegetarian product with its therapeutic values has a promising consumer appeal and market potential

especially for large vegetarian population in India and abroad. The unique biochemical engineering techniques adopted to retain the antidiabetic activities in preparation of Cadalmin™AHe assures higher shelf life. The product is safe from toxicity studies on experimental subjects.

Preclinical trials showed no toxicity related significant changes in renal or hepatic function, hematological indices and serum biochemical parameters in experimental subjects. The results demonstrated a lack of test substance-related general organ or systemic toxicity and hypertensive disorders following oral administration at a dose as high as 2000 mg/kg/d. Cadalmin™Antihypertensive extract has no side effects (LD_{50}> 4000 mg/kg BW) as proved from preclinical and acute/long term chronic toxicity studies on experimental subjects.

Time dependent shelf life studies were conducted to identify changes in bioactivity profile of the product in an accelerated shelf-life study, which revealed that no significant reduction of anti-angiotensin converting enzyme-I activities and content of active principles of the formulation after end of study period. This product is available in encapsulated form and is to be used orally. Large scale extraction of active principles from raw material was optimized in a factory unit.

Sixth nutraceutical product from ICAR-CMFRI

Cadalmin™ Antihypertensive extract **(Cadalmin™AHe)** is the sixth in the series of nutraceutical products and fifth from seaweeds from ICAR-CMFRI. Earlier, the Institute has developed and commercialized four nutraceutical products from seaweeds and one product from green mussels. *'Cadalmin™Green Algal extract (Cadalmin™GAe)'* and *'Antidiabetic extract (Cadalmin™ADe)'* were developed from seaweeds as green alternatives to synthetic drugs to combat rheumatic arthritic pains and type-2 diabetes respectively. *'Cadalmin™ Antihypercholesterolemic extract (Cadalmin™ ACe)'* and *'Cadalmin™ Antihypothyroidism extract (Cadalmin™ATe)'* to combat dyslipidemia and hypothyroidism respectively are other two nutraceutical products from seaweeds which were commercialised to a biopharmaceutical company. *'Cadalmin™green mussel extract (Cadalmin™GMe)* is the nutraceutical product which was developed from green mussel to combat arthritis.

The rich diversity of seaweeds represents an untapped reservoir of bioactive compounds with valuable pharmaceutical and biomedical use. Seaweed has long been part of the traditional diet of coastal communities. Various nutraceutical or functional food supplements and biomedical products from seaweeds provide a myriad of benefits for human health and multiple life threatening diseases. ICAR-CMFRI is the pioneering marine research institute to work in the frontier area of marine bioprospecting/bioactive molecule discovery from seaweeds and development of high value nutraceutical products as dietary supplements and health management against various lifestyle diseases.

In 2014, production of seaweeds through mariculture (44% of all aquaculture) was estimated at about 27 million tons wet weight, registering annual growth rate of 8% and valued at 7 billion US$ (FAO 2016). Seaweed mariculture in India remained in experimental trials until recently. World seaweed production through mariculture is expecting an increase of 9.8 million tons by the year 2025.

ICAR-CMFRI is in the process of developing more health products from the underutilized seaweeds. The institute is also in the process of standardizing and promoting seaweed farming all along the Indian coasts as a livelihood option for the coastal communities. This is expected to compensate fishermen during lean seasons.

Cadalmin™ AHe was released by Dr Trilochan Mohapatra, Secretary, DARE and DG, ICAR on 25 May 2019. The product is ready for out-licensing to the pharmaceutical/biopharmaceutical company.

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