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FORMULATION, DEVELOPMENT AND EVALUATION OF *DICTYOTA DICHOTOMA* EXTRACT MEDICINAL SEAWEED CAPSULES DELIVERY SYSTEM AS AN ADVANCED PHYTOTHERAPY APPROACH FOR CANCER

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ABSTRACT
The Algae *Dictyota Dichotoma* is seaweed widely distributed in marine environment, other parts of the world, such as in Yemen, the algae are a commercially important and renewable marine resource that are being studied on the use of many industrial applications such as in food, cosmetics, dye, and medicine. Brown algae are a premising object in the food industry and prophylactic and clinical medicine. Complementary and alternative medicine has been used widely in various populations for various purposes, including emotional support and improvement of quality of life. Nowadays biologically active compounds of algae (phlorotannins, carotenoids, alginic acid, fucoidan, peptides) are being demonstrated to play a significant role in prevention of certain degenerative diseases, such as cancer, inflammation, arthritis, diabetes and hypertension. Therefore, immense biochemical diversity of algae derived from active components become a rich source of novel chemical entities for the use as functional ingredients in many industrial applications such as functional foods, pharmaceuticals and cosmeceuticals. In the present study the algae *Dictyota Dichotoma* were collected from Red Sea coast, Hodeida. It was prepared six formulation of *Dictyota Dichotoma* extract capsules. It was concluded that the best formulation F4 of *Dictyota Dichotoma* medicinal seaweed capsules delivery system as an advanced phytotherapy approach for cancer according to *in-vitro* dissolution was found to be 96.1% within 10 minutes in acid medium.

KEYWORDS: *Dictyota Dichotoma*, Anticancer, Formulation, Capsule, Algae, Phytotherapy.

INTRODUCTION
Cancer is one of the most important diseases in the world, and cancer chemotherapy is the gold standard of treatment. Most of the anticancer drugs currently used in chemotherapy are cytotoxic to normal cells too. Seaweed is a marine macro alga comprised many genus's and species. These marine organisms have been traditionally used as food sources and therapeutic agents, especially in some parts of Asia such as Japan, Korea, and China.[1-3]

Fig. 1: The Algae *Dictyota Dichotoma.*

Algae *Dictyota Dichotoma* is seaweed widely distributed in marine environment, other parts of the world, such as in Yemen, as shown in Figure 1, some Chemical constituents of brown algae Seaweed is one of the largest producers of biomass in marine environment and is a rich arsenal of active metabolites and functional ingredients with valuable beneficial health effects. Pervious studies showed being a staple part of Asian cuisine, investigations on the crude extracts of Phaeophyceae or brown algae revealed marked antitumor activity, eliciting a variety of research to determine the active ingredients involved in this potential. The sulfated polysaccharide of fucoidan and carotenoid of fucoxanthin were found to be the most important active metabolites of brown algae as potential chemotherapeutic or chemopreventive agents. Besides that, numerous microalgae are reported to contain various essential compounds. These chemical diversities can be explored for potential drug development. Algae provide many vitamins including:

A, B_1, B_2, B6, niacin and vitamin C and are rich in iodine, potassium, iron, magnesium, and calcium. Polysaccharides, also a major compound used for food, fodder and therapeutics are also obtained from marine algae (Rhodophyceae). Poly unsaturated fatty acid which are precursor of eicosanoids, regulating normal physiology and body homeostasis are found in many macroalgae. Seaweed dietary values are due to the existence of many compounds, such as vitamins, fatty acids, minerals, trace elements, dietary fibers included soluble, insoluble and total dietary fibers, and amino acids they produce several kinds of secondary metabolites such as phlorotannins, fucoidan, alginate, laminaran, and terpenoids that have shown a wide range of biological effects. [4-14]

Seaweeds contain sulphated polysaccharides, fucoidan, polyelectrolytes like alginates, carrageenans, agarans etc. The species rich in polysaccharides mainly belong to brown algae or pheophycea family and are prevalent in coastal area. Ascophyllum, Porphyra and Palmaria are few brown algal species which contain are a rich source of biologically active isoprenoids. In previous studies reviewed about 200 diterpenoids, belonging to 15 chemical classes, have been isolated from *Dictyota* spp. Some of these compounds are reported to display significant cytotoxic, antiviral, feeding-deterrent and antifouling activities or were useful for chemotaxonomic and biogenic studies of the genus, *Dictyota*. Algae contain diverse types of sterols, fucosterol, cholesterol and sitosterol are found in chlorophyceae; brassicasterol, cholesterol, fucosterol are found in phaeophyceae; desmosterol, sitosterol, cholesterol, fucosterol, clionasterol etc. are found in Rhodophyceae. Fibers found in different algal groups are also diverse, cellulose, mannans and xylan are water insoluble whereas agars, alginic acid, porphyrin, furonan and laminarin are important water-soluble fibers mostly found in seaweed. [10-24]

Algae in both micro and macro form have tremendous scope for exploring bioactive compounds. They have been used traditionally for medicinal purposes in India, China, Japan, Korea, Ireland, Wales and other countries. Brown seaweeds (macro algae) are reported to have anti-inflammatory, antitumor and immunostimulant activities. Macroalgae are prolific sources for numerous natural compounds with promising potential for both preventions. and treatment of several diseases including cancer and diabetes. These seaweed's fibers contain some valuable nutrients as well as pharmacologically active substances, and nowadays there is a lot of interest in seaweed meal, functional foods and nutraceutical for human consumption. These phytochemical diversities of microalgae nowadays are being used as alternative food supplement and the algal compounds are reported to have anti-viral, anti-bacterial and anti-fungal activity. There is a huge scope to obtain novel bioactive compounds from these unexplored large biomass of sea organisms. Previous studies showed that the trying to encompass the beneficial role of marine macro and micro weeds primarily against uncontrolled cell proliferation and subsequent tumor formation. More than 50 % of marine cyanobacteria are possibly available for intending bioactive elements which are powerful in either slaughtering the disease cells by instigating apoptotic demise, or influencing the cell signaling over the enactment of the portions of protein kinase-c group of indicating chemicals. Biologically active compounds of algae (phlorotannins, carotenoids, alginic acid, fucoidan, peptides) are being demonstrated to play a significant role in prevention of certain degenerative diseases, such as cancer, inflammation, arthritis, diabetes and hypertension.[10-24]

Nowaday's cancer incidences are in increasing trend and therefore instant effective therapies are needed to control these malignancies. Normally rapidly dividing cells are controlled by anticancer drugs, but the normal cells are also affected and pattern in which it is determines the side effects. Auspiciously numerous preceding readings have shown that the anticancer activities of non-toxic biological macromolecules are higher than conventional chemotherapy drugs. Marine algae are obliged as significant sources of natural bioactive substances and there has now emerged a new proclivity towards isolating and identifying such compounds and constituents from algae. Molecular and cellular level studies on algae have indicated that algae derived bioactive are potent cancer inhibitors. Macro algal crude extracts or their products have high cytotoxic activity on brain, renal and colon tumors inhibit the growth and invasion of several tumor cell lines, impedes lung metastasis and prolongs survival in mice or lead to apoptotic body formation in the CT-26 murine colon cancer cell line.[25-28]

Complementary and Alternative Medicine (CAM) and Cancer[28-38]

Cancer is caused mainly due to mutation or malfunction of cell cycle controlling machineries. Standard treatment for curing cancer including chemotherapies, coupled with radiation therapies are available but sometime they are associated with severe side effects, as for example, radiation therapies partially disrupt patient's normal immune systems. Nausea, vomiting, loss of appetite are also common side effects of those standard treatment. Cancer is a leading cause of death worldwide which requires a multidisciplinary treatment approach. Safety and efficacy of many of the modern therapies have been well established but still use of complementary and alternative medicine (CAM) is on rise among cancer patients.

Treatments for cancer are multidisciplinary which requires the skills of a team of experts. Conventional treatments are those that are extensively merged into the modern health care system. They are usually considered as Evidence Based Medicines (EBM) i.e. the safety and efficacy of these therapies have been well established

through clinical trials. The use of CAM for health and for healing purposes has long existed in human society. In the modern era, therapies which are now used to complement or as an alternative to conventional medicines, were the only way of cure in ancient times.

In the modern era of the 21st century, many of the under developed countries such as African and some of the south East Asian countries rely solely on CAM as a source of treatment. A systematic survey on complementary and alternative medicine (CAM) uses among cancer patients in North America, Europe, and Australia/New Zealand found that the United States has the highest CAM use among cancer patients. CAM therapies include medication therapies (which involve the use of herbal medicine, animal parts, and/or minerals) and non-medication therapies carried out primarily without the use of medication (such as acupuncture or manual therapy). Populations throughout Africa, Asia, and Latin America use traditional medicine to help meet their primary health care needs. In addition to being accessible and affordable, traditional medicine is also often part of a wider belief system, and is considered integral to everyday life and well-being. In Europe and North America, CAM is increasingly being used in parallel to allopathic medicine, particularly for treating and managing chronic disease. Concerns about the adverse effects of chemical medicines, a desire for more personalized health care, and greater public access to health information fuel the increasing use of CAM in many industrialized countries.

CAM obtained from marine flora specially from both micro- and macro algae reported to have active anti-carcinogenic potentiality. Marine algae constitute about 90% of marine organism's diversity, at the same time contain diverse types of biomolecules; such as vitamins, minerals, dietary fibers, sterol, polyphenols, different types of polysaccharides and numerous secondary metabolites. These chemical diversity and huge unused biomass of algae can be explored for drug development. Algal biodiversity was previously used commercially to make nutraceuticals, food supplements, meals, gelling substances. Recent study showed that their active anti-carcinogenic potentiality. Most of the algal extracts induce cancer cell death by inducing apoptosis or preapoptosis either by caspase dependent or caspase independent pathways. Seaweeds or marine algae have long made up a key part of the Asian diet and are also consumed in other parts of the world, such as in Ireland and Wales. Seaweed has often been used as a food for people who are sick and has been credited with health-giving properties. Today, seaweed supplements for human use are usually considered to be sources of iodine or minerals but may offer other therapeutic benefits. Brown algal preparations have been used as detoxifying agents.

The iodine and other elements in the seaweeds inhibit absorption of similar radioactive elements by the body. In addition, there is some chelation of contaminants such as Strontium 90 by alginates in seaweeds. Brown algae as either food or in supplement form may provide useful additional therapy for treating hepatic viral infections and some cancers. Other benefits include mild antihypertensive- and cholesterol-reducing effects. Used with caution, so as not to exceed the maximum iodine or arsenic intakes, these algae also provide valuable mineral supplementation. The National Center for Complementary and Integrative Health (NCCIH) defines CAM as a group of diverse medical and healthcare systems, practices, and products that are not generally considered part of conventional medicine. A similar definition given by the WHO, where CAM is defined as "a broad set of health care practices that are not part of that country's own tradition and are not integrated into the dominant health care system" The WHO defines complementary and alternative medicine (CAM), or so-called traditional medicine, as follows: "a comprehensive term used to refer both to traditional medical systems such as traditional Chinese medicine, Indian ayurveda and Arabic Unani medicine, and to various forms of indigenous medicine.

Table 1: Biochemical Composition of *Dictyota Dichotoma*.

Composition	%
Carbohydrate (% dry wt.)	25.1 ± 0.5
Protein (% dry wt.)	7.6 ± 0.5
Lipid (% dry wt.)	2.8 ± 0.1
Reducing Sugar (mg/g)	4.03 ± 0.2
Total Amino Acids (mg/g)	46.9 ± 1.0
Vitamin C (mg/g)	0.3 ± 0.03
Total Phenolic Content	1.88 ± 0.02

Seaweed or macro algae provide a great variety of metabolites and natural bioactive compounds with antimicrobial activity, such as polysaccharides, polyunsaturated fatty acids, phlorotannin's and other phenolic compounds, and carotenoids species of brown algae belonging to family Dictyotaceae have been shown to be a rich source of interesting biologically active diterpenoids of versatile chemical classes as shown in Table 1.

Dictyota Dichotoma as anticancer in the nanomedicine is the most revolutionized procedure to a greater extent in days to come. Among other nanoparticles Ruthenium compounds are well known for their high relevance as drug candidates, though they have very little in common with the already existing Platinum-based drugs. By a rapid synthetic method Ruthenium nanoparticle.

Capsule Delivery System[39-46]

Capsules are solid-dosage forms that are available in two types -hard (two-piece) or soft (one-piece). The major component of the capsule shell is gelatin, although other polymers have been investigated as capsules. Capsules may be filled with arrange of formulation types, including powders, tablets, semisolids (hard capsules)

and liquids (soft capsules). The formulation that is included within the capsule contains several components, each of which is present to facilitate the manufacture or to control the biological performance of the dosage form.

Advantages of Capsules*:* Ease of use due to the fact that it is smooth, slippery and easy to swallow. Suitable for substances having bitter taste and unpleasant odor. As produced in large quantities it is economic, attractive and available in wide range of colors. Minimum excipients required. Little pressure required to compact the material. Unit dosage form and easy to store and transport.

Disadvantages of capsules*:* The hygroscopic drugs cannot be filled in capsules. They absorb water present in the capsule shell and hence make it very brittle, which ultimately breaks into pieces and the concentrated preparations which need previous dilution are unsuitable for capsules because it may lead to irritation in stomach if administered as such.

In the present study the *Dictyota Dichotoma* freeze - dried extract powder solid dosage form medicinal seaweed capsules delivery system were prepared and evaluated as an advanced phytotherapy approach for cancer.

MATERIALS AND METHODS

Collection and Drying

The *Dictyota Dichotoma* algae were collected from Red Sea coast, Hodeida. The methanol extract of *Dictyota Dichotoma*, was prepared and gift from (Prof Dr. Amina El-Shaibany, Professor Dr. of Pharmacognosy, Department of Pharmacognosy, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen). Hard Gelatin Capsules (Size 00; Color: Red body. Black Cap), Starch, Colloidal Silicon Dioxide (Aerosil), Magnesium Stearate, Microcrystalline Cellulose MCC, Lactose, Talc, Crospovidone, Hydrochloric Acid (0.1NHCl), pH6.8 buffer Solution, and Methanol. were obtained from Sigma Aldrich. All chemicals used were all of analytical grade and other materials were gift from (Shaphaco Pharmaceutical Industry Company-Yemen).

Formulation and Evaluation of *Dictyota Dichotoma* Extract[47-76]

Determination of The Organoleptic Properties of Extract

The following organoleptic properties of *Dictyota Dichotoma* extract materials such as physical appearance, odor and taste were inspected and assessed using the natural senses (e.g. eyes, nose, mouth).

Determination of The Solubility of Extract

Solubility is an important factor for drug absorption. The equilibrium solubility of the freeze -dried extract of *Dictyota Dichotoma* determined as follows: A saturated solution obtained by stirring excess extract powder solute with distilled water for few hours at the required temperature (25C°, 37C°) by using water bath until equilibrium has been attained. Samples are withdrawn every 30minutes and filters. Absorbance of the sample was measured at 288nm for *Dictyota Dichotoma)* using UV Spectrophotometer. The absorbance reading should increase until one gets to a maximum when equilibrium is reached. This indicates the time required for equilibration.

The solubility was obtained by the following equation.
Solubility = (weight of initial powder - weight of dried residue) / volume of solvent x100%.

Table 2: Composition of Formulations of *Dictyota Dichotoma* Extract Capsules.

Ingredients	Quantity Per Capsule(mg)					
	Formulation Code					
	F1	F2	F3	F4	F5	F6
***Dictyota Dichotoma* Extract**	150	150	150	150	150	150
Microcrystalline Cellulose MCC	205.8	205.8	205.8	205.8	203.8	210.8
Lactose	20	20	20	20	20	20
Crospovidone	2.5	---	10	15	10	5
Starch	111.7	114.2	99.2	96.7	101.2	101.7
Talc	---	---	5	2.5	5	2.5
Mg. Stearate	5	5	5	5	5	5
Aerosil	5	5	5	5	5	5

Formulation of *Dictyota Dichotoma* Extract Capsules[47-76]

Determination of the dose of dried extract per capsule the amount of the active ingredient in the capsule 150mg. Determination of the toxic dose and the safety dose of the extract. According to previous study they observed (No toxicity for mouse when give it 5g). The selection of the capsule size, the filling machine, the filling method and the excipients were carried out in which 150mg of this drug mixed with excipients place manually in a separate size "00" capsules, then taken four capsules daily to provide the desired dose. The selection of the capsule size, the filling machine, the filling method and the excipients are described as shown in Table 2.

Evaluation of the *Dictyota Dichotoma* Extract Capsules[47-76]

***In-Vitro* Dissolution Studies of *Dictyota Dichotoma* Extract Capsules**

The basket method was used. The quantitation of the amount of extract material dissolved was measured based on uv absorbance measured at 288nm, the wavelengths for maximum uv absorbance of solutions of the *Dictyota Dichotoma* extract was determined.

RESULTS AND DISCUSSION

The dried extract of *Dictyota Dichotoma* obtained as shown in Figures 2 to 5.

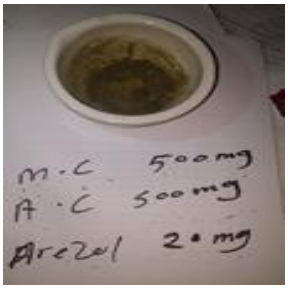

Fig. 2: Drying of *Dictyota Dichotoma* Extract.

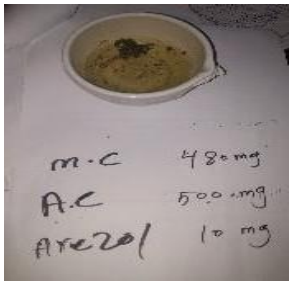

Fig. 3: Drying of *Dictyota Dichotoma* Extract.

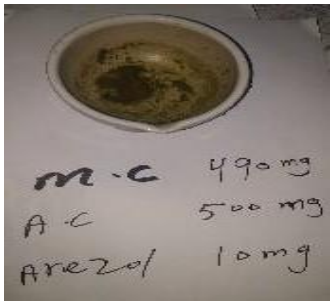

Fig. 4: Drying of *Dictyota Dichotoma* Extract.

Fig. 5: Drying of *Dictyota Dichotoma* Extract.

The Organoleptic Properties of The Freeze -Dried of *Dictyota Dichotoma* Extract

As shown in Table 3, the organoleptic properties of the freeze -dried extract.

Table 3: The Organoleptic Properties of *Dictyota Dichotoma* Extract.

Organoleptic properties	Description
Taste	Strong Bitter
Color	Brown
Oder	Fishy Smell
Touch	Sticky

Table 4: The Solubility of *Dictyota Dichotoma* Extract in Different Medium.

Medium	Solubility of *Dictyota Dichotoma* Extract
Distal water	Insoluble
Buffer pH6.8 (Potassium Dihydrogen Phosphate)	Freely Soluble
Acid 0.1N of HCl	Freely Soluble

The results of the solubility studies of *Dictyota Dichotoma* extract are freely soluble in acid medium and buffer pH6.8 and insoluble in water as shown in Table 4.

Drug Release of *Dictyota Dichotoma* Extract Capsules

The results of the *in-vitro* dissolution studies of *Dictyota Dichotoma* extract capsules as shown in Table 5, the dissolution percentage of F4 it was found to be 96.1% within 10 minutes in acid medium. while in buffer medium the dissolution percentage of F4 it was found to be 21% within 10 minutes as shown in Table 6.

Table 5: Drug Release Percentage of Formulation of *Dictyota Dichotoma* Extract Capsules in Acid Medium.

Formulation Code	Time (min)	Drug Release%
SD	10	100%
F1	10	6.8%
F2	10	62.7%
F3	10	41.6%
F4	10	96.1%
F5	10	41.1%
F6	10	41.0%

Table 6: Drug Release Percentage of Formulation of *Dictyota Dichotoma* Extract Capsules in Buffer pH6.8 Medium.

Formulation Code	Time (min)	Drug Release%
SD	10	100%
F2	10	7.5%
F3	10	5.7%
F4	10	21%
F5	10	5.2%
F6	10	5.4%

CONCLUSION

It was concluded that the best formulation F4 of *Dictyota Dichotoma* medicinal seaweed capsules delivery system as an advanced phytotherapy approach for cancer according to *in-vitro* dissolution was found to be 96.1% within 10 minutes in acid medium.

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