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Medicinal plant derived drugs and their treatment for human diseases like cancer: A review

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Abstract

Several medicinal plants have been popularly known and widely used to cure various diseases throughout the planet since ancient times. Various types of plants have been found to cure different kinds of human diseases effectively. Several research are focused on finding specific compounds from medicinal plants that have effective medicinal properties in curing human diseases. Finding the bioactive compounds specific to a disease could help in understanding the properties of the compound towards a disease and thereby its application with more precision and convenience. Understanding the characteristics of the bioactive compound can help in large scale production to be commercially available globally as per the demands and it can direct to design for synthetic production. It will benefit in several ways in terms of reducing the amount of intake as lesser amount would be needed, reducing restriction of availability as the plant grow at certain environmental conditions and overcome inconvenience of transport/portability and preservation and unseasonal availability of the plant. In this short review, plant derived natural products; anticancer properties of cumin from *Curcuma longa subsp* and the importance of medicinal plants such as *Cronton caudatus subsp* are highlighted.

Keywords: Medicinal plants; Bioactive compounds; Cancer; curcumin; *Cronton caudatus subsp*

1. Use of plants for curing human diseases

Since time immemorial various types of medicinal plants have been used for treating different kinds of human diseases and the recent developments in modern therapeutics have stimulated the use of natural products throughout the world. Now a day, educated people and healthcare professionals take great interests on herbs for medicinal uses. Medicinal plants contain a wide diversity of secondary metabolites with different biological activities which can generate potent bioactive molecules necessary for health enhancement. However, there is lack of scientific data proving the efficacy and safety of medicine, their chemical and biological properties etc. Therefore, several researches are being undertaken and in great progress for scientific understanding about the properties of herbs including its identification, effectiveness, therapeutic dosage, toxicity, standardization and regulation etc. WHO has also stated that traditional medicine is popular in every region of the world and its use is rapidly expanding even in developed countries [1]. Over 60% of the world's population and about 80% in developing countries directly depend on medicinal plants for healing purposes [2]. Notably, traditional herbal preparations account for 30–50% of the total medicinal consumption in China and annual global market for herbal medicine is over 60 billion USD, annually [1]. The reasons for using medicinal plants include affordability, accessibility, and low cost [3], less side effects and its effectiveness [4,5]. As the medical science continue to advance, modern medicine today utilizes active compounds isolated from leaf/ stem/ bark/ root of the plants to prevent or relieve symptoms and return to normal; and about 80% of the active ingredients indicate a positive correlation between their modern therapeutic use and the traditional uses [6].

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It may be noted that about 35,000 plants have been screened by The National Cancer Institute (NCI) for potential anticancer activities, among which about 3,000 plant species have been demonstrated with reproducible anticancer activity [4]. The data is available at http://www.ars-grin.gov/ duke/. Presently the main target of many scientists in cancer research is to build preventive and curative properties based on the ancestral knowledge of traditional medicine plants. It deals with extraction of the active compounds, purifies it, and then followed by chemical modification the structural level to increase their cytotoxic and antiproliferative potential [7]. The goal is to test them in vitro to define their bioactivity and use them later in clinic to prevent or treat incurable diseases such as cancer [8,9]. Recent findings have demonstrated medicinal plants synthetizing cardiac glycosides which are well known for their medicinal properties in triggering various canonical and noncanonical cell death modalities [10, 11,12]. There are already some natural compounds that have been identified and used in cancer research triggering the essential hallmarks of cancer that leads to apoptotic cell death.

2. Plant derived or natural products in drug discovery

Historical records evidenced that Natural products and their structural analogues have given a major contribution to pharmacotherapy, particularly in cancer and infectious diseases. Notably, more than 80% of the population of developing countries depends on plants for their medical needs [13]. However, the use of medicinal plants in the form of crude extracts has several issues to be taken into account. Because the amount of the bioactive compound(s) from plants may vary with both the locality and the season in which they are collected. And the bioactive molecules of many plants are powerful poisons when taken in excess, whereas if the plant extract contains a lower content of bioactive compound(s) than usual, suboptimal dosage may not be effective. There is also rapid loss of medicinal properties of many plants on storage [13]. Subsequently, not only the bioactive molecules, crude extracts from many medicinal plants may contain other constituents which have harmful effects.

However there are challenges for natural products in drug discovery in terms of technical barriers to screening, isolation, characterization and optimization etc. To overcome these challenges, in recent years, several technological and scientific developments including improved analytical tools, genome mining and engineering strategies, and microbial culturing advances have been developed. In fact, interest in natural products is being rejuvenated, for tackling antimicrobial resistance [14]. Natural products have special features in comparison with conventional synthetic molecules, which confer both advantages and challenges for the drug discovery process. Natural products are characterized by a vast scaffold diversity and structural complexity [15]. They usually have a higher molecular mass, a larger number of sp3 carbon atoms and oxygen atoms, but fewer nitrogen and halogen atoms, higher numbers of H-bond acceptors and donors; lower calculated octanol–water partition coefficients (cLogP values, indicating higher hydrophilicity) and greater molecular rigidity compared with synthetic compound libraries [16,17,18,19,20]. These differences can be advantageous in such that the higher rigidity of natural products can be valuable in drug discovery tackling protein–protein interactions [21]. In fact, NPs are a major source of oral drugs 'beyond Lipinski's rule of five' [22]. There is increasing significance of drugs that do not conform to this rule, which is demonstrated by the increase in molecular mass of approved oral drugs, over the past 20 years12 [15]. By logic, natural products are structurally 'optimized' by evolution to serve specific biological functions [16]. It includes the regulation of endogenous defense mechanisms and the interaction (often competition) with other organisms, which explains their high relevance for infectious diseases and cancer [15]. Natural products remain as promising sources for the discovery of scaffolds with high structural diversity and various bioactivities that can be directly developed or used as starting points for optimization into novel drugs. The scientific and technological advances can be driving force for NP-based drug discovery and thereby major contributions to human health and longevity.

Indeed, the search for a new drug from nature is based on a biological and ecological rationale and the fact that natural products have provided many effective drugs leads forward to providing more natural based drugs in the future. In fact, therapeutically active phytoconstituents isolated from higher plants have been providing novel and clinically active drugs. Some of the drugs from natural products that have been discovered and widely used include older ones such as quinine and morphine and newer ones such as paclitaxel, camptothecin, etoposide, mevastatin and artemisinin [23]. Another reason for the need of discovery of novel drugs from nature is because many isolated molecules are quite complex, and would not be obtained by a simple synthetic approach. Most natural origin bioactive compounds are secondary metabolites which are species-specific chemical agents that can be grouped into various categories. Biological screening of 'crude' extracts to identify a bioactive 'hit' extract, then further fractionation to isolate the active natural products, are routine procedure in starting natural product based drug research. In order to create libraries that are compatible with high-throughput screening, crude extracts can be pre-fractionated into sub-fractions that are more suitable for automated liquid handling systems. Furthermore, fractionationation methods can be adjusted for allowing to preferentially contain compounds with drug-like properties (typically moderate hydrophilicity) into the sub-fractions [15].

One of the most emerging tool or a typical protocol to isolate a pure chemical agent from natural origin is *bioassay-guided fractionation*. In this process the step-by-step separation of extracted components are based on differences in their physicochemical properties and assessments of the biological activities, which are followed by next round of separation and assaying [24]. Bioassay guided fractionation of plant extracts is subjected to chromatographic separation techniques for the isolation of biological active molecules. It thus provides the strategies for the fractionation of plant extracts based on biological activity rather than on a particular class of compound and thereby the recent interest in the plant kingdom as a potential source of new drugs. The chemical examination usually follows the isolation of the active fraction [25]. The key to the success of discovering naturally occurring therapeutic agents relies on bioassay-guided fractionation and purification procedures.

3. Curcumin as an anticancer bioactive compound.

There are many vegetables which contain bioactive compounds having anticancer potential such as isothiocyanates in cabbage, lycopene in tomatoes and flavonoids in carrots etc [26]. One of the most investigated plant products is the curcumin (polyphenol) from *Curcuma longa* which is commonly used as spice/ingredient in the curry in India. A detailed mechanism underlying the effect of curcumin in the proliferation arrest and disruption of cell cycle control leading to apoptosis is demonstrated by Srivastava et al (2007) [27]. Their studies showed curcumin inducing apoptosis in prostate cancer cells through Bax translocation to mitochondria and caspase activation and thus enhancing the therapeutic potential of TNF-related apoptosis-inducing ligand. Curcumin induces cell cycle arrest at G1/S phase in two prostate cancer cell lines, androgen-sensitive LNCaP and androgen-insensitive PC-3, and then followed by induction of apoptosis. It also induces expression of CDK inhibitors such as p16/INK4a, p21/WAF1/CIP1 and p27/KIP1, and inhibited expression of cyclin E and cyclin D1 and hyperphosphorylation of retinoblastoma (Rb) protein. Further, lactacystin (an inhibitor of 26 proteasome) blocks curcumin-induced down-regulation of cyclin D1 and cyclin E proteins, suggesting that their regulation is at the posttranslation level. It is possible that cyclin D1 and cyclin E suppression by curcumin may inhibit CDK-mediated phosphorylation of pRb protein. Subsequently, siRNA blocks curcumin-induced apoptosis by inhibiting p21/WAF1/CIP1, thus establishing a link between cell cycle and apoptosis.

On the other hand, curcumin was also found to effectively inducing paraptosis in malignant breast cancer cell lines such as DA-MB-435S, MDA-MB-231, and Hs578T cells, by promoting vacuolation that results from swelling and fusion of mitochondria and/or the endoplasmic reticulum (ER) [28]. Protein synthesis inhibition by cycloheximide blocked curcumin-induced vacuolation and subsequent cell death. The levels of paraptosis inhibitor proteins such AIP-1 or Alix protein were progressively downregulated in curcumin-treated malignant breast cancer cells which the overexpression of these proteins attenuated curcumin-induced death in these cells. ERK2 and JNK activation were positively associated with curcumin-induced cell death. Mitochondrial superoxide also acts as a critical early signal in curcumin-induced paraptosis, whereas proteasomal dysfunction was mainly responsible for the paraptotic changes associated with ER dilation. These observations were not found in normal breast cells, including mammary epithelial cells and MCF-10A cells indicating that curcumin-induced paraptosis may provide novel insights into the mechanisms underlying the selective anti-cancer effects of curcumin against malignant cancer cells [28].

It may also be noted that curcumin has emerged as one of the most powerful chemopreventive and anticancer agents [29]. Its' biological effect range from antioxidant, anti-inflammatory to inhibition of angiogenesis and possesses specific antitumoral activity. Curcumin has been shown to possess anti-angiogenic properties due to down regulation of proangiogenic genes such as VEGF and angiopoitin and a decrease in migration and invasion of endothelial cells. Curcumin could down regulate NFkB which is highly chemosensitive and inhibit IKB kinase thereby suppressing proliferation and inducing apoptosis.

Natural products are also involved in the PARP-1 dependent cell death is dependent on the generation of PAR that triggers nuclear translocation of apoptosis-inducing factor (AIF) to result in caspase-independent cell death which is known as "parthanotos" [30,31]. The parthanatos cell death regulation pathway includes PARP-1 overactivation, PAR accumulation, nuclear translocation of the mitochondrial protein apoptosis-inducing factor (AIF), and large-scale DNA cleavage. The overactivation of PARP-1 lead to the production of free PAR polymer or poly ADP-ribosylated acceptor proteins which are then translocated to the cytosol and mitochondria where they may lead to externalization of phosphatidylserine and dissipation of the mitochondrial membranpotential. Mitochondrial intermembrane flavoprotein AIF synthesized in the cytoplasm as a 67 kDa precursor, contains a predicted mitochondrial localization signal at its N-terminal presequence and during its translocation into the mitochondria, AIF is cleaved at the Met53/Ala54 sites into the mature 62 kDa form that then localizes at the inner membrane with its N terminal exposed to the matrix and its C-terminal exposed to the intermembrane space [32]. The mature AIF 62 kDa is further processed to 57 kDa form upon stimulation by death [33]. There are other natural compounds that have shown to significant role

in parthanotos pathways leading to tumor cell death for example Catechins (-(epicatechin-3-gallate(EGCG)), polyphenols present in Camellia sinensis(L.) Kuntze/Cha [34].

There are multiple categories of natural compounds which could interfere with cancer-specific cell signaling pathways [35, 36, 37, 38]. Apoptosis inducing agents did not always lead to efficient treatment approaches in clinical practice, since the cancer cells tend to develop multiple resistance mechanisms against apoptotic cell death and therefore finding alternative pathways of cell death induction is necessary for improving cancer cell death-inducing strategies [39]. Compounds that induce non-apoptotic cell death mechanisms will have the ability to circumvent classical antiapoptotic resistance mechanisms. It also may be noted that natural compound-induced morphological alterations occurring during non-canonical cell death induction apoptosis and autophagy were traditionally considered as the most prominent cell death or cell death-related mechanisms. Although the herbal medicine has been used in the Middle East and European countries from ancient days and many advance countries have considered traditional herbal treatment as an official treatment for cancer, the recent report by the World Health Organization (WHO) showed, only 5–15% of the herbs have been investigated to detect their bioactive anticancer compounds [4, 40, 41]. And it is highly important to understand the different biological activities of the diversity of secondary metabolites which can generate potent bioactive molecules for health enhancement towards a more precise treatment with the efficacy and safety of medicine. Ancestral knowledge from traditional medicine more recently led to extraction of active compounds, purification and / or chemical modification of natural scaffolds in order to increase their therapeutic potential.

4. *Cronton caudatus subsp* anticancer properties

Another well-known medicinal plant *Croton caudatus Geiseler* (local name: Kam-Sabut). The oral administration of the leave extract has been first experimented at Saikot, Churachandpur district of Manipur by Mr. Chawilen to himself, therefore name as “Chawilen damdawi (medicine)” after him [42].The plant is also known as the miracle plant of Saikot and Damdawi by the locals. The plant is widely available in South East Asia including Northeast region of India, Manipur and Mizoram states another species is found in South India is identified as Croton caudatus Geisel. Its’ roots are purgative, and roots/stems/leaves are used for treating ardent fever, convulsions, malaria, numbness, and rheumatoid arthritis and have been known to have less toxic [43,44,45,46]. The leave extract was also found to have free radical scavenging and antioxidant activities [47] and bioactive compounds such as alkaloids, cardiac glycosides, flavonoids, saponins, phytosterols, phlobatannins, phenolics and terpenoids are also present in this plant [45]. Anticancer properties have also been suggested in a few studies [16,48,49,50,51].

5. Conclusion

The deeper understanding of cancer continue to progress from the ancient time until today along with the advancement of technology and there is still need of further understanding.This review covers a very small area of medicinal biotechnology but highlights importance of medicinal plants in general, the need of further knowledge to treat disease with precision, importance of bioactive compounds in drug discovery and commercial availability, and two well-known plants having anticancer properties. The available compounds, from natural products and its derivatives need to be studied; to draw a conclusive remark, further studies is very necessary. The discovery of peclitaxol took 20 years [53] and its very effectiveness with the advancements in the study of its pathways led to increase in efficacy of the drug. The surge in the compounds has opened a Plethora of avenues questioning us researchers and the necessity to channel to the right targets to be beneficial for human use.

Compliance with ethical standards

Disclosure of conflict of interest

Authors declare that no conflict of interest.

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