Medicinal plants in the treatment of cancer

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ABSTRACT

The purpose of this paper is to present a review of highly developed medicinal usages of plants in the treatment of cancer. In the last decades, the cancer treatment has been included in this range of plant use, due to plant active substances. Active substances or secondary metabolites are generally known for their widespread application. When it comes to the cancer treatment, these substances affect the uncontrolled cell division. Therefore, the plants which are the source of these substances are proved to be irreplaceable in this field of medicine. This paper deals with some of the most significant plants well known for their multiple aspects of beneficial medicinal influence. The group of the plants described is comprised of the following species: Taxus brevifolia (Taxaceae), Catharanthus roseus (Apocynaceae), Podophyllum peltatum (Berberidaceae), Camptotheca acuminata (Cornaceae), and Cephalotaxus harringtonia (Cephalotaxaceae). The comprehensive description of the plants in this paper includes the morphological characteristics, the features and the representation of the molecular structures of active substances, the particular influence that these active substances have and the general importance of the substances as seen from the aspect of cancer treatment mostly with reference to the impacts on cell cycle.

Keywords: Active substances, cancer treatment, medicinal plants.

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INTRODUCTION

For very long time a large number of medicinal plants have been used as culinary spices, in the preparation of food and various beverages. Other, even more important usage is related to the treatment of many diseases of the human organism. Through medical and pharmaceutical history, nature was confirmed to be an excellent and reliable source of pharmaceutically active substances, including anticancer agents. It is well established fact that plants have always been the useful source of cancer prevention compounds. More than 60% of currently used anticancer chemotherapeutics are derived in one way or another from natural sources, including medicinal plants. The major categories of plant-derived compounds that have medicinal properties are secondary metabolites from plants. The main secondary metabolites in plants are phenolic acids, flavonoids and alkaloids. These active substances perform a number of protective functions in the human organism and are involved in important anti-oxidative, anti-allergic, anti-biotic, hypoglycaemic and anti-carcinogen activities (Stanković et al. 2010, Quideau et al. 2011, Stanković et al. 2011a, Stanković et al. 2012a). Due to their natural origin, the anticancer drugs obtained from plants are of greater benefit in comparison to the synthetic ones. Mechanism of anticancer activity which is based on suppression of mitosis by facilitating the stability of microtubules, causes cells to undergo apoptosis and disruption of signal transduction etc. It is commonly used in chemotherapy of lungs, ovarian and breast cancer. A large number of known medicinal plants has anticancer effects and is widely used or is under investigation (Sadeghi-Aliaabadi et al. 2009).

Each of the represented species contains secondary metabolites which are significant in the treatment of many diseases. The secondary metabolites of the species *Taxus brevifolia* are used in the treatment of several types of cancer (Rowinsky 1997, Skeel 1999). The metabolites of the species *Catharanthus roseus* are proved to have beneficial effects in the treatment of cancer and leukemia, (Gidding et al. 1999, Aslam et al. 2010). The species *Podophyllum peltatum* contains metabolites which are indispensable both in cancer therapy and therapy for some other ailments (Foster 1989, Clarke 1990). *Camptotheca acuminata* and active substances have given important contribution to the field of cancer treatment (McDonald 1997, Heron 1998). The metabolites of the species *Cephalotaxus harringtonia* are proved to have antibacterial and antifungal effect (Watanabe and Fukao 2009), and are widely used for various types of leukaemia therapy (Cragg and Newman 2005).

**Plant secondary metabolites and their anticancer activity**

In addition to the very significant and necessary biological effects in the process of plant response to negative influence of environmental factors, i.e. conditions of stress, secondary metabolites of the plants in isolated conditions, outside the organism, show more or less pronounced biological activity. Isolated secondary metabolites, either separately or together express their biological activity in both *in vitro* and *in vivo* conditions (Atmani et al. 2009, Pereira et al. 2009, Quideau et al. 2011).

Secondary metabolites of the plants in the *in vitro* conditions, as well as other active substances, express their activities on several levels of biological systems, beginning with simple towards very complex ones. They may influence isolated bio-molecules, isolated sub-cellular structures and cells (whether unicellular organisms or isolated cells of multicellular organisms), as well as the isolated tissues (Stanković and Topuzović 2012, Stanković et al. 2012b, Ćurčić et al. 2012).

In the *in vivo* conditions, they express their effect on the whole organism, and that effect may be positive, mostly of therapeutic character, or negative, mostly toxic. The biological activity of secondary metabolites of plants is based on their capability to react with numerous regulatory molecules and other cellular and sub-cellular structures, thus having positive or negative effect on many metabolic processes. The effect of secondary metabolites is most often manifested through the control of enzymatic reactions, control of hormone activity, gene expression, cellular transport, cell division, immune response and a series of other physiological processes. Acting with its stimulation or inhibitory mechanism, secondary metabolites express anti-oxidative, anti-microbial, anti-proliferative, apoptotic, anti-inflammatory, anti-hypertensive, neuroprotective and many other activities (Briskin 2000, Katalinich et al. 2005, Gordaliza 2007, Hasani-Ranjbar et al. 2010, Karsha and Lakshmi 2010, Stanković 2011, Stanković et al. 2011b, Stanković et al. 2011c, Stanković et al. 2012c). Secondary metabolites of plants in both *in vitro* and *in vivo* conditions may have effect on uncontrolled cell division, which in some cases results in neoplasia, i.e. local, non-typical, autonomous and uncontrolled growth of a tissue that is called tumor which can be benignant or malignant. The mechanism of anti-tumor activity of secondary metabolites of plants is diverse - some inactivate carcinogens, block cell cycle in G0/M...
phase, inhibit proliferation, induce apoptosis, have antioxidative activity, inhibit angiogenesis, control activities of certain enzymes included in regulation of cell cycle and regulate transport through the cell membrane (Ren et al. 2003, Khantamat et al. 2004, Khoo et al. 2010, Duangmano et al. 2010).

DISCUSSION

Medicinal plants for anticancer therapy

In numerous in vitro and in vivo experiments during pre-clinical and clinical examinations of anti-cancerous activities which plant active substances perform, it was determined that some plant species were indispensable source of anti-cancerous substances.

Pacific yew

*Taxus brevifolia* Peatle (Taxaceae) (Figure 1). Pacific yew is an evergreen shrub from the group of conifers, bushy forms or trees of medium height (Guchelar et al. 1994). Physiological development of plant mostly reposes on conditions in which the plant grows and impacts to which the plant itself is exposed. Therefore, in adequate coastal conditions the plant reaches up to 60 cm in diameter as well as 15 m in height, whereas in environments with no appropriate elevation, the plant is only several metres high. The plant has widely spread and highly deep roots. The colour of plant bark differs depending on the degree of plant development. Plant twigs are usually rose-coloured, whereas older plants are reddish brown in colour. Leaves are linear, dark green, and of acute tip. The surfaces of leaves differ depending on what is on them. There is a median ridge on the upper and 2 yellow green bands on the lower surface. The length of leaves varies from 8 to 35 mm and their breadth ranges from 1 to 3 mm. Male and female strobili are positioned on the underside of branches. The seed, whose length varies from 5 to 6.5 mm, is of ovoid shape, and is completely encased in red aril which has 10 mm in diameter and is considered not to be poisonous as opposed to the rest of its overground parts. It is vital to mention that, as a part of their basic structure, seeds have oily endosperm and a small embryo (Abrams 1940, Viereck and Little 1972, Rudolf 1974, Bolsinger and Jaramillo 1990, Earle 2002).

More active anticancer substance isolated from *T. brevifolia* is Taxol® (Paclitaxel) which belongs to the class of taxane diterpenoid compounds (Kingston 1998). Main anti-cancerous chemical source in *T. brevifolia* is stem bark. Taxol was discovered in the bark and (Figure 2) shows excellent results in the cancer treatment (Wani et al. 1971). It is proven, through its structural modifications, that the bioactivity of taxol is highly sensitive to the assignment of certain functions. Most of taxol modifications have either harmful, or beneficial effect, at least in the conditions of in vitro analysis (Kingston 1998). Paclitaxel is considered to be a natural substance which has significant role in stabilizing microtubules and is used on a regular basis for treatment of several types of cancer among which are lung cancer, breast cancer, ovary cancer, bladder cancer, and so on and so forth (Rowinsky 1997, Skeel 1999). The stabilization of microtubules is performed through a process of depolymerization of microtubules (Schiff and Horwitz 1980). Paclitaxel is also quite often used in the treatment of polycystic kidney disease (Woo et al. 1994). It is proven to be very efficient in therapies for coronary diseases (Tanimoto et al. 2007). According to certain studies, the increase in number of coronary diseases directly influenced demand for paclitaxel (Lasala et al. 2006). Paclitaxel impedes the cell proliferation and blocks mitosis as a part of a cell cycle. Cell proliferation occurs in G2-M phase of the cell cycle whereas some other anticancer substances show effects in G1-S phase (Manfredi et al. 1981). There are more than 350 different taxol structures which have so far been isolated from the species of genus *Taxus*. Pharmacy has provided a description of a very effective method of taxol chemical synthesis (Baloglu and Kingston 1999).

![Figure 1. Taxus brevifolia (copyright to Jason Hollinger CC-BY-2.0).](image)

Periwinkle

* Catharanthus roseus (L.) G. Don (Apocynaceae) (Figure 3). Madagascar periwinkle originates from Madagascar Island (Sakarkam and Desmukh 2011). It is a shrub whose usual height is 1 m. Glossy green, hairless, oval or oblong leaves are arranged on the
opposite pairs. Their length ranges from 2.5 to 9 cm, whereas their width can reach up to 3.5 cm. The petiole is short and its length can vary from 1 cm to 1.8 cm. The color of the flower differs and can be white or dark pink with a center of a darker red color. The basal tube is usually with a corolla whose diameter can reach up to 5 cm with five petals like lobes. The fruits are a pair of follicles with length up to 4 cm and breadth of 3 mm at most (Frode and Medeiros 2008).

**Figure 2. Molecular structure of paclitaxel.**

**Catharanthus roseus** contains more than 130 different compounds, including approximately 100 monoterpenoid indol alkaloids (Pereira et al. 2010), caffeoylquinic acids and flavonol glycosides (Ferreres et al. 2008). Main anti-cancer chemical source in *C. roseus* are leaves (Gajalakshmi et al. 2013). Two main alkaloids of this plant are vincristine and vinblastine (Figure 4) (Duflos et al. 2002). Vincristine and vinblastine are used for the treatment of lymphoma and leukemia (Van der Heijden et al. 2004). They are powerful antineoplastic agents (Svoboda and Blake 1975). Vinblastine sulphate is considered to be particularly beneficial in the treatment of neuroblastoma, carcinoma of breast and lungs, Hodgkin’s disease, and choriocarcinoma. Vinkristin sulphate is very efficient against Wilkins’s tumor, neuroblastoma and acute leukemia in children (Gidding et al. 1999, Aslam et al. 2010). Vinblastine blocks endothelin proliferation, chemotaxis and spreading on fibronectin, all of which are essential steps in angiogenesis (Vacca et al. 1999). Vinkristin causes destabilization of microtubules by binding to tubulin and blocking the polymerisation (Wang et al. 1999). The efficiency of alkaloids isolated from *C. roseus* is based on the reaction of alkaloids with tubulin and disruption of microtubule function, particularly of microtubules comprising the mitotic apparatus, directly causing metaphase arrest (Himes 1991).

Active components of this plant, except anti-cancerogenic effect, possesses antiviral (Farnsworth et al. 1968), antibacterial (Carew and Patterson 1970, Prajacta et al. 2010), antifungal (Jaleel and Panneerselvam 2007), and antioxidant effects (Kumar et al. 2012, Tiong et al. 2013). The plant is also used for the active treatment of fever, sore throat, malaria, diabetes as well as for the regulation of a menstrual cycle (Gajalakshmi et al. 2013). It is also characterized by hypoglycemic, analgesic and vasodilatory effects (Nayak and Lexley 2006).

**Mayapple**

*Podophyllum peltatum* L. (Berberidaceae) (Figure 5), Mayapple is an upright herbaceous plant growing from 45 to 60 cm high, of low or moderate branches. The leaves are palmately arranged and up to 30 cm wide. The flowers are of white colour, and form the v-shaped axel of the stem. Mature fruits are of yellow colour, between 3.5 and 6.5 cm long, of ovoid shape and may contain up to 25 brown, flattened and rough seeds, each in an aril (Krochmal et al. 1974). It
is significant to mention that all parts of *P. peltatum* are poisonous except for the ripe fruit (Maqbool 2011).

Main anti-cancer chemical source in *P. peltatum* are leaves (Maqbool 2011). Well known compounds of this species are podophyllotoxin and alpha and beta peltanin. *P. peltatum* contains high concentrations of podophyllotoxin which can be used for the production of synthetic derivates such as etoposide and teniposide (Figure 6). Podophyllotoxin possesses antimitotic, anticancer and immunostimulant effects (Loike et al. 1978, Morales et al. 2001, Pugh et al. 2001). Etoposide and teniposide are characterised with a remarkably beneficial effect in the treatment of lung cancer and cancer of testicles (Foster 1989). Teniposide affects microtubules, reacts with proteins, and modifies tubulin GTP binding thus influencing DNA, which makes them suitable for the cancer treatment (Bjorkholm 1990). CHP 82 is a synthetic compound which can be obtained from podophyllotoxin and is commonly used in the arthritis treatment (Lerndal and Svensson 2000). The effect of podophyllotoxin on mitosis is considered to be the same as in the case of colchicine (Biesele 1958). Podophyllotoxin and its derivates (teniposids and etoposids) impede the process of lymphocyte proliferation (Mansson et al. 1988), as they affect DNA topoisomerases (Long and Stringfellow 1988).

Podophyllotoxin is famous for its antifungal and antimalaric effects (Lerndal and Rosen 1988, Pugh et al. 2001). It is used for the treatment of psoriasis (Lerndal and Rosen 1988). Alpha and beta peltanin are known as laxatives and as an adequate means in the treatment of warts and skin cancers (Krochmal et al. 1969). The extracts of *P. peltatum* are frequently used for the treatment of several serious diseases such as bronchitis, proctitis, gastroenteritis or dysentery (Clarke 1990).

**Cancer tree**

**Camptotheca acuminata** Decne. (Cornaceae) (Figure 7), Cancer tree is a deciduous tree which grows up to 25 m. The trunk can reach even 60 cm in diameter and is completely without branches in the lower parts. The leaves are alternately arranged, of ovate shape, pinnate veined, of a simple built and of a maximal length of 15 cm. The white plant flowers are either solitary or arranged in panicles of 3 to 6. There are ten white stamens and five-toothed calyx. The fruit is usually of 2.5 cm length and when dry it normally gets brown colour (Perdue et al. 1970).

Main anti-cancer chemical source in *C. acuminata* are fruit, but bark and leaves are also used for this purpose (Li and Zhang 2014). The main alcaloid isolated from this plant, or to be more precise from its
trunk and cortex is camptothecin (Figure 8) (Vincent et al. 1997, Nirmala et al. 2011). Anticancer activity of camptothecin is based on the inhibition of DNA topoisomerase, which thus impedes the DNA replication in the infected parts of cells (Kjeldsen et al. 1992). Camptothecin is frequently used as a basic chemical substance in the forming of derivates such as topotecan and irinotecan. Together with some other natural and synthetic derivates, these are used in the prevention and treatment of breast cancer, pancreatic cancer, cancer of the ovaries and other types of human cancer (McDonald 1997, Heron 1998). The extracts of C. acuminate showed significant effect when it comes to treating retroviruses such as the human immunodeficiency virus or equine infectious anemia virus. In these cases, camptothecin inhibits the transcription of the viral promotor (Li et al. 1994).

![Figure 8. Molecular structure of camptothecin.](image)

The seed oil of this species has the antimicrobial and antioxidant quality (Wang et al. 2011). It is proved that the derivates of camptothecin represent the powerful means against the pathogenetic fungi (Del Poeta et al. 1999).

It is also well established fact that the younger the plant leaves are the greater the production of camptothecin is. However, there are some indications that drought can in certain cycles enhance or, at least influence the production and biosynthetic activities of camptothecin. Minimal quantities of water and the plants from different geographical locations were used to provide evidence for the beneficial effect drought can have on the increase of camptothecin concentration (Liu et al. 2000, Li et al. 2002).

Japanese plum

*Cephalotaxus harringtonia* K. Koch (Cephalotaxaceae) (Figure 9), Japanese plum yew is a conifer species originating from Japan. Its overground part is either bushy or a low tree. It is well-known in horticulture and popular culture as a plant of a rather fine texture, and it is thus widespread (Powell et al. 1972). It is an evergreen, upright shrub growing in small communities, flowering in spring. Its average height ranges from 1.5 to 3 m. It grows and slowly develops its highly dense branches. The leaves are of green colour, and have less than 5 cm leaf blade, needle-like shape and parallel venation. The size of its oval, fleshy and brown fruit varies from 2.5 and 7.5 cm (Gilman 1999). The overground parts of this species contain the alkaloid omacetaxine (Figure 10) which is significant for its anticancerous activity and is used in the therapy of chronic myelogenous leukemia (Powell et al. 1972).

![Figure 9. Cephalotaxus harringtonia (copyright to BotBln CC-BY-SA 3.0).](image)

Main anti-cancer chemical source in *C. harringtonia* are leaves (Choi et al. 2003) but some other parts are used as well (Powell et al. 1972). The well known alkaloids of this plant are cephalotaxine, harringtonine, homoharringtonine, isoharringtonine (Huang and Xue 1984). The alkaloid homoharringtonine shows cytotoxic effects on KB, HeLa, and L cells (Baaske and Heinstein 1977). Its cytotoxicity is based on the inhibition of the protein synthesis through affecting ribosomes in the cancer cells. Homoharringtonine blocks the progression of the cells from G1 phase to S phase as well as from G2 phase to M phase (Zhou et al. 1995). These alkaloids have certain effect on the various types of acute leukemia when they are dosed intravenously (Miah et al. 1998). Secondary metabolites of this plant possess antibacterial and antifungal effect (Watanabe and Fukao 2009).

**CONCLUSIONS**

Secondary metabolites of the presented plants have proved potential in the field of cancer treatment. Structural modelling of the metabolites results in the creation and development of substances which constitute the basis of modern and progressive medicine. The appropriate summary of both the plant substances created in this way and their effects
follows. The most important substance obtained from *T. brevifolia* is paclitaxel which impedes cell proliferation and blocks mitosis. The beneficial effect of the alkaloids of *C. roseus* mostly consists of the impact on tubulin which leads to polymerisation and destabilisation of microtubules. Teniposide substance from *P. peltatum* influences microtubules and modifies tubulin GTP binding thus necessarily changing the DNA. Camptothecin obtained from *C. acuminate* inhibits DNA topoisomerase and thus directly affects DNA replication in the infected cells. The basic effect which several alkaloids of *C. harringtonia* show is the inhibition of protein synthesis in cancer cells. Taking into consideration all the presented facts, it is regarded as utterly beneficial to continue research of these plants in the direction intended to improve the previously obtained results, that is, as a part of modern scientific developmental tendencies.

**Molecular structures**

Molecular structures of all presented compounds were made using ChemCraft programme.

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**References**


Plantas medicinais no tratamento de câncer. O objetivo deste trabalho é apresentar uma revisão sobre os usos medicinais altamente desenvolvidos de plantas no tratamento de câncer. Nas últimas décadas, o tratamento do câncer tem sido incluído nesta gama de utilização de plantas, devido às substâncias ativas das plantas. As substâncias ativas ou metabolitos secundários são geralmente conhecidos pela sua ampla aplicação. Quando se trata do tratamento do câncer, estas substâncias afetam a divisão celular descontrolada. Portanto, as plantas que são fontes destas substâncias são provas de serem insubstituíveis neste campo da medicina. Este artigo trata de algumas das plantas conhecidas mais importantes por seus múltiplos aspectos da influência benéfica medicinal. O grupo das plantas descritas é composto das seguintes espécies: Taxus brevifolia (Taxaceae), Catharanthus roseus (Apocynaceae), Podophyllum peltatum (Berberidaceae), Camptotheca acuminate (Cornaceae), e Cephalotaxus harringtonia (Cephalotaxaceae). A descrição completa das plantas no presente documento inclui as características morfológicas, as características e a representação das estruturas moleculares de substâncias ativas, em particular a influência que essas substâncias ativas apresentam, e a importância geral das substâncias, como pode ser visto a partir do aspecto do tratamento do câncer, principalmente com referência aos impactos sobre o ciclo celular.

Palavras-chave: Active substances, cancer treatment, medicinal plants.