Chapter 45

Uncaria tomentosa: A promising source of therapeutic agents for prevention and treatment of oxidative stress and cancer

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Introduction

The reactive species, in particular, those of the oxygen (ROS) and nitrogen species (RNS), play roles in the activation of signaling pathways in animal and plant cells in response to changes in environmental conditions of intra- and extracellular compartments.

During the last two decades, extensive research has revealed some of the mechanisms by which continued oxidative stress (OS) can lead to chronic inflammation and subsequently to diseases including cancer, cardiovascular failure, diabetes, neurological, and pulmonary diseases.

Reactive species and mediators of inflammation can cause genetic lesions such as mutations in tumor suppressor genes leading to genome instability and change in gene expression patterns. These modifications have been described in cancer diseases before the development of cancer itself. However, ROS and mediators of inflammation can perform their action of either pro- or antitumorigenic activities increasing the complexity of cancer biology.

Cancer is a multistage process in which three steps are recognized: initiation, promotion, and progression.[1] OS, ROS, and RNS affect all the stages of carcinogenesis: they are able to induce DNA damage, during the initiation stage, provoking structural modifications of the DNA and gene mutations. During the promotion stage, ROS can induce aberrant gene expression, alteration in cell-cell interaction or signal transduction pathways, which lead to uncontrolled cell proliferation and apoptosis failure. At the progression stage, OS takes part in neoplastic development inducing further DNA damage to the initiated cell population. To complicate matters, OS also intervene in the transition from the inflammatory state to the initiation of the cancer process. In fact ROS are produced in high amounts by inflammatory cells. Further, the tumor cells produce factors able to attract inflammatory cells. Therefore OS, chronic inflammation, and cancer are closely linked and their activity creates a closed circle destined to progressively aggravate the pathological state.[2, 3] Several recent studies both in cellular systems and animals have been conducted to find out novel substances with antioxidant activities, with the aim to reduce chronic inflammation injuries and hinder the neoplastic promoters.

Thorough attention by means of chemopreventive must be given to patients with oxyradical overload diseases to stop, or even reverse, carcinogenesis before cancer becomes clinically observable. Several agents are able to interfere with redox cell signaling pathways, including nutraceuticals from vegetables, fruits, spices, and plants.

South America, particularly Brazil, Colombia, and Peru, is the source and reservoir of many medicinal plants. Asháninka priests Sancoshi educated by their mentors in complete seclusion in the forest are traditionally meant to be able to recognize good spirits in individual plants that can be used to eliminate disturbances between body and spirit, and thereby restore health. According to folklore, one of the plants containing good spirits is *Uncaria tomentosa*. It grows as a woody vine and is found at the base of tall trees in the rainforest, winding its way up around the tree with curved thorns that resemble *cat's claws* at the base of its leaves. The root and bark extracts have traditionally been used by priests to treat various diseases, including asthma, arthritis, rheumatism, abscesses, gastric ulcers, inflammation, menstrual irregularity, viral infections, and cancer.

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Antitumor and antioxidant effects of *U. tomentosa* have been shown in in vitro systems and some animal models. However, the adoption of different extraction protocols (e.g., aqueous vs organic solvents) has produced different mixtures of bioactive compounds making the systematic evaluation of *cat's claw* biological activities quite problematic. However, *U. tomentosa* has been largely investigated for its antineoplastic properties, which is not surprising considering that cancer is regarded as a chronic inflammatory disease. To date, compounds isolated from *cat's claw* have shown growth inhibitory activity in vitro against a wide range of human cancer cell lines, by increasing the cell death and DNA damage.

The present chapter is an overview of the biological effects ascribed to *U. tomentosa* extracts and derived metabolites. They have been shown to suppress tumorigenesis in preclinical models.[4] Therefore, *U. tomentosa*-derived compounds offer great promise for its use in cancer prevention and therapy by targeting redox-sensitive pathways.

Applications to other cancers or conditions

In this chapter, we reviewed how *U. tomentosa* extracts can have effects as anticancer and antioxidant factors.

Several human cancer cell lines were studied to evaluate the anticancer properties of *U. tomentosa* extracts. *U. tomentosa*-induced apoptosis is the main mechanism involved in antitumor efficacy of this plant. Some adenocarcinoma from colon, cervix, breast, and lung and melanoma cell lines were found to be sensitive to the apoptotic effects of *U. tomentosa* extracts. Furthermore, SAOS, MCF7, and HeLa human cancer cell lines were also sensitive to the *U. tomentosa* apoptotic action, activating it via caspase3. Interestingly, *U. tomentosa* extracts have been reported to inhibit the proliferation of HL-60 and K562 human leukemia and Raji EBV-transformed B lymphoma cell lines without inducing apoptosis.

U. tomentosa has been demonstrated to enhance chemotherapy-induced apoptosis, establishing a role for cancer patients as a complementary therapy.

Moreover, human epidermoid cancer cells (A431) were found to be sensitive to aqueous extract of *U. tomentosa* bark, antagonizing the oxidative stress-induced DNA repair, supporting the use of the extract for the treatment of precancerous and early forms of squamous cell carcinomas.

Reports have shown that *U. tomentosa* extracts and preparations are able to inhibit tumor growth and metastasis in mouse and rat models. Authors have identified in the interference on the metabolism of ROS and in some redox processes the mechanisms responsible for the beneficial effects.

Chemotherapeutics are used for the treatment of many cancers, whose side effects are in many cases related to alteration in the cellular part of the blood, leading to erythropenia and leukopenia. *U. tomentosa* has been used as an adjuvant in the treatment of breast cancer to reduce toxic effects and restore cellular DNA damage. Even in patients with colorectal cancer, *U. tomentosa* has minimized the deleterious effects of chemotherapy treatment. The beneficial effect is assumed to be due to the ROS's scavenging ability.

Uncaria tomentosa

As reported by the World Health Organization (WHO) about 80% of the population use medicinal plants as alternative or complementary procedures for the treatment of their diseases. Among the plants the *U. tomentosa* [Willdenow ex Roemer and Schultes (Willd) de Caundolle (DC)], known as "*cat's claw,*" has been used in South American countries, over the centuries, as a traditional medicine for its several supposed health benefits.[5] Already since 1994 the WHO recognized *U. tomentosa* as an important medical plant authorizing its marketing. In fact in Europe the use of *U. tomentosa* in different forms, such as capsules, extracts, and tea has been introduced, for the complementary treatment of patients affected by cancer or viral diseases.

The *U. tomentosa* is a tropical vine belonging to the family of *Rubiaceae*. It is a scrambling liana, up to 20–30 m long, and with a stem over 25 cm in diameter.[6] This plant is a thick woody vine that grows at an altitude of 500–600 m above sea level, in high forests with abundant insolation, from the Amazon rainforest and other tropical areas of South and Central America[7] (Figs. 1 and 2). The presence of hook-like thorns, growing along the vine in a leafy pattern, resembles the claws of a cat and for this reason, it is known as "cat's claw" (Fig. 3).

U. tomentosa was first described in 1830 and first studied in Perù by the German biologist Brell in 1950.[8] In Peru, many native tribes such as the Aguaruna, Ashaninka, Cashibo, and Shipibo use *U. tomentosa* for its multiple properties in the medical field. Keplinger, studied the medicinal system of the Ashaninka, one of the most numerous indigenous people of South America, to learn more about the healing properties found in cat's claw extracts[9]; he spent several years with this population and discovered that Sanchosha priests attributed miraculous powers to some plants. In 1980, Kindberg[10] reported in the Ashaninka dictionary a prickly plant, probably referable to *Uncariae*. So according to this folklore, one of

FIG. 1 Traditional method of drying barks of *Uncaria tomentosa*. Traditional method of air drying of barks. The arrow indicates a particular bark of *U. tomentosa*. *(Photograph courtesy of Prof. Domenico Carotenuto.)*

FIG. 2 Stem with and without bark of *Uncaria tomentosa*. The stem of *U. tomentosa* is observed in the presence and absence of bark. *(Photograph courtesy of Prof. Domenico Carotenuto.)*

FIG. 3 Leaves of *Uncaria tomentosa* with characteristic hooked thorns. At the base of *U. tomentosa* leaves are the hooked thorns (arrow), reason for the name "*uña de gato*.". The arrow indicates a particular hooked thorn of *U. tomentosa*. *(Photograph courtesy of Prof. Domenico Carotenuto.)*

these plants was *U. tomentosa*, whose root and bark extracts were traditionally used by Sanchosha to treat various diseases including asthma, arthritis, rheumatism, inflammation, and viral infections.[11]

Botanical classification of *Uncaria genus*

In 1978, Ridsdale[12] reported that the *Uncaria genus* is constituted by a total of 39 species, 34 of them are distributed in Southeast Asia, 3 in Africa, and 2 in tropical America. Andersson and Taylor in 1994[6] reported about 60 species of Uncaria distributed worldwide. Actually, about 40 currently known species and most of the native species are distributed in tropical areas such as Asia, Africa, the Mediterranean, and the neotropics.[13]

Regardless of the number of species known so far, all of them have the same general characteristics, in fact, all are lianas with monopodial main shoots and more or less horizontal patent.[6] The two American species of Uncaria are *U. tomentosa* and *U. guianensis* [(Aublet), Gmell], and according to Peruvian scientists, they have often been confused.[5] *U. tomentosa* is characterized by densely tomentose buds, and the meshing and tightening of the longer hairs, which help stipules to remain connected to each other along the margins. Moreover, the thorns are straight, very sharp, and insensitive sickles.[14]

Chemical composition of *U. tomentosa*

U. tomentosa is used in Perù and Europe and since 1994 the WHO recognized this plant as an adjunctive treatment for cancer and other diseases.[15] The edible part of *U. tomentosa* is the bark that in the pharmaceutical industry is processed into capsules, tablets, ointments, and even tea.

Heitzman et al.[7] isolated about 50 different components from all plant parts of this species and 35 of which have been identified in only a couple of other species. In particular, three classes seem to play an important role in cat's claw activity. These compounds are the alkaloids, quinovic acid glycosides, and polyhydroxylated triterpenes (Table 1).[16] The alkaloid content can vary 10–40-fold depending on cultivation techniques and the season when the plant is harvested[17] (Fig. 4).

The oxindole alkaloids are considered the main active compounds responsible for the medicinal activities and are classified into two chemotypes: tetracyclic and pentacyclic indole alkaloids.[18] The pentacyclic indole alkaloids stimulate the cellular immune system, the tetracyclic indole alkaloids the central nervous system, and have an antagonistic effect when combined.[18]

The chemical composition of *U. tomentosa*, and in particular the concentration of certain analytes present, can vary from the collection area of the plant, seasonality, maturity, and extraction method. The presence of the chemical components in *U. tomentosa,* in particular of oxindole alkaloids, is affected during seasons by changes in environmental factors such as water supply, temperature, and light.[19]

Oxidative stress

Free radicals and, in particular, ROS play an important role in the regulation of metabolic activity and the functioning of certain organs. They are produced by the mitochondria during normal aerobic metabolism.[20] ROS, which include the hydroxyl radicals ($^{\bullet}OH$), superoxide anion ($^{\bullet}O_2^-$), hydrogen peroxide (H_2O_2), are highly reactive molecules due to the presence of an unpaired electron in their outer shell. They have a very short half-life in the range of nanoseconds to

TABLE 1 Chemical composition of *Uncaria tomentosa*.

Oxindole alkaloids
Indole alkaloids
Quinovic acid glycosides
Pyroquinovic acid glycosides
Organic acids
Proanthocyanidines
Sterols
Triterpenes

FIG. 4 Cut stems of *Uncaria tomentosa*. Stems of *U. tomentosa* traditionally cut from a native inhabitant. *(Photograph courtesy of Prof. Domenico Carotenuto.)*

milliseconds. ROS are produced as a consequence of natural cell machinery and participate in the normal function of a cell. The normal production of ROS is necessary for the functions of the body, while excessive ROS production is harmful. For instance, physiological and low levels of ROS in the spermatozoa play an important role in processes such as capacitation, hyperactivation, acrosome reaction, and sperm-oocyte fusion, thus ensuring appropriate fertilization, whereas high levels of ROS may determine sperm pathologies, such as ATP depletion and loss of sperm motility and viability.[21]

However, when ROS production overcomes cellular antioxidant defenses overcoming the physiological range, they cause deleterious effects due to oxidative stress which results in the oxidation of lipids, proteins, carbohydrates, and nucleotides.[22] OS is a particular kind of chemical stress, which is induced, locally and/or systemically, by an excess of potentially oxidant reactive species; it appears to be a health risk factor for aging disorders and several diseases in humans and in animals.[23]

The production of free radicals by cells can increase considerably due to external stimulation; physical agents (ionizing radiations and UV rays), chemicals (ozone, polycyclic aromatic hydrocarbons or drugs), biological agents (bacteria), pollution can induce an increase in the production of free radicals through a specific metabolic stimulation.[24] A large amount of ROS is able to attack any substrate with which they come into contact, tearing from them the electron or electrons needed to reach their own stability. This triggers radical chain processes which, if not blocked in a timely manner, can cause serious consequences on the plan, first functional, then also structural. The cell is the first target of oxidative damage. The damage, initially cellular, if prolonged through time, spreads to the tissues, organs, and then becomes systemic.

Indeed, evidence shows that OS can influence the onset of diseases such as diabetes, cardiovascular diseases, depression, anxiety, neurodegenerative diseases, early senescence, inflammation, and cancers.[25]

Many studies have been carried out to counteract the oxidative conditions with the use of specific antioxidants.[26–29] The cellular antioxidant defense systems are able to control the deleterious effects of ROS.[24, 30, 31] Antioxidants are groups of substances of different chemical nature and present at low concentrations with respect to the substrate, and act with different mechanisms by inactivating or eliminating the free radicals. They can be classified into enzymatic and nonenzymatic. The enzymatic antioxidants include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX). SOD catalyzes the dismutation reaction of the superoxide anion into hydrogen peroxide and is found in the mitochondria, cytosol, and extracellular space.[32] CAT catalyzes the conversion of H_2O_2 to O_2 and H_2O, acting mainly in the endoplasmic reticulum, peroxisomes, mitochondria, and the cytosol of several cell types.[33] Glutathione peroxidase (GPX), which is located mainly in the mitochondria,[32] catalyzes the reduction of H_2O_2 and organic peroxides.

Among the nonenzymatic antioxidants are vitamins (C and E), carotenoids, carnitine, cysteine, some metals, taurine, and albumin.[34]

Exogenous antioxidants can also be classified according to their mechanism of action into three groups: vitamin C, vitamin E, vitamin A, carotenoids, and phenolic compounds that react directly with free radicals transforming them into less reactive molecules; those that perform a chelating action against metal ions such as iron and copper avoiding Fenton's reactions (albumin, transferrin, and ceruloplasmin); and minerals that are structural components of antioxidant enzymes as copper, zinc, and selenium.[24] Fig. 5 shows the power hierarchy of antioxidant pyramid. Endogenous enzyme antioxidants have a higher antioxidant capacity and are located at the top of the pyramid.

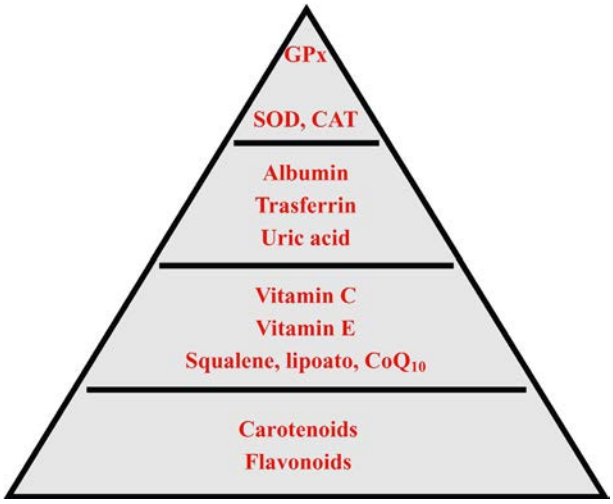

FIG. 5 The antioxidant pyramid. The power hierarchy of antioxidant pyramid is shown in this figure. Endogenous enzyme antioxidants have a higher antioxidant capacity and are located at the top of the pyramid. *(From Tafuri S, Cocchia N, Landolfi F, Iorio EL, Ciani F. Redoxomics and oxidative stress: from the basic research to the clinical practice. In: Wu B, editor. Free radicals and diseases, vol. 8. Intechopen; 2016. p. 149–169. https://doi.org/10.5772/64577.)*

Epidemiological evidence shows that the diet and an appropriate lifestyle can play a very important role in the modulation of OS and, in particular, on the deleterious effects that OS can have on organisms.

Indeed, through the diet the organism introduces both oxidizable substrates and antioxidant substances which can prevent the formation and progression of degenerative diseases thus underlying the strict relationships among diet, OS, and pathologies.

Some plants from South America are increasingly used for their therapeutic properties because they produce metabolites that modulate the effects of the OS.[28, 29, 35] Such metabolites are polyphenols, sterols, and alkaloids, some of which are considered important nonenzymatic antioxidants able to scavenge free radicals and protect cells from OS.[36]

Oxidative stress and *U. tomentosa*

U. tomentosa, the tropical rainforest vine plant, distributed naturally from Peru to Guatemala,[37] is used in raw form or as extracts of root, stem bark, or leaves. Depending on different extraction protocols adopted, e.g., aqueous vs ethanol at various temperatures, Uncaria extracts may have different compositions, making systematic research on the biological activities of *cat's claw* problematic. To overcome the variability in Uncaria extract composition due to the application of different extraction protocols, a method has been suggested to standardize the preparations based on *U. tomentosa*, by using a defined ratio of polar and nonpolar solvents.

To standardize the protocol for Uncaria extract preparation, Pilarski et al.[38] suggested an easy method for their extraction that produced reproducible antioxidant activity mainly ascribable to polyphenol content. The analysis of alkaloids was carried out on the bark of *U. tomentosa*, while ethanol and aqueous bark extracts were prepared for the quantitative determination of tannins, the total phenolic compounds, and the antioxidant capacity. The evaluation of the results has evidenced that the ethanol bark extract has greater antioxidant activity and is more effective than aqueous extract.

Phyto-complex is a set of active and inactive molecules present in the plants. Each plant species requires, for its growth, a certain soil and climate, in terms of altitude, latitude, mean temperature, average rainfall, light availability, and physicochemical soil properties. Climatic conditions and soil characteristics can certainly affect the availability of metabolites necessary for the compound biosynthesis. For instance, a plant can lose the ability to synthesize specific bioactive molecules if it grows outside its specific habitat. Thus, the knowledge of the agricultural techniques, the territory, and of the phyto-complex pattern of a specific plant in relation to environment can help to obtain a standardized extract indispensable to improve the herbal product final quality and ensure the clinical effectiveness.

Vera-Reyes et al.[39] have highlighted how the OS elicitation can influence the gene expression of some enzymes in *U. tomentosa* and direct the metabolism toward the synthesis of biomolecules, in this case alkaloids with antioxidant activity, which defend the plant against adverse environmental conditions. Similarly, OS status in *U. tomentosa* cell cultured in a

bioreactor, due to generation of ROS, induced pentacyclic monoterpenoid oxindole alkaloid (MOA) accumulation. MOA is known to act as immunomodulatory, cytotoxic, antileukemic, and anti-AIDS. Interestingly, the aim of the study was to use biotechnological tools to produce MOA as an alternative to chemical synthesis, that results too much elaborate and to avoid deforestation.[40]

Cancer cells are sensitive to OS, whereby the mechanism of action for many cancer chemotherapeutic drugs involves ROS-mediated apoptosis. Many studies have evaluated the effects of substances, herbal plants, or drugs on neoplastic cells with the aim of tracing back to the apoptosis induction via OS. In fact, hydroalcoholic extract of *U. tomentosa* is able to enhance chemotherapy-induced apoptosis, establishing a role for cancer patients as complementary therapy.[41] Also, Ciani et al. reported the ability of an aqueous bark extract of *U. tomentosa* to induce oxidative DNA damage and antagonize the mechanism of DNA repair in A431 cancer cells (human epidermoid cancer cells) with a defective G1/S checkpoint with a consequent accumulation of G2/M arrested cells followed by massive apoptosis.[42]

By now it is everyone's opinion that the environment must be safeguarded and that pollution, in general, can cause problems for the health of humans, animals, and other living organisms. One of the causes of pollution is the presence of xenobiotics, including pesticides, which are the reason for many harmful effects on health. Some studies assessed if *U. tomentosa* extracts are able to counteract the deleterious effects of pesticides responsible for OS. Catechol and 2,4-DCP, derived from 2,4-dichlorophenoxyacetic (2,4-D) transformation, used for the cultivation of rice, cereals, and so on, are hormonal herbicides characterized by high toxicity, persistence of residues in the environment and capacity to bioaccumulate in living organisms. *U. tomentosa* leaf and bark extracts were tested to verify if they possess antioxidants properties against the OS provoked by 2,4-DCP and catechol in red blood cells.[43] Although no striking effect was observed on most of the parameters studied, *U. tomentosa* was found to be effective in preventing oxidation of hemoglobin by decreasing the amount of ROS in parallel with the onset of hemolysis caused by 2,4-DCP. Furthermore, no direct action of the extracts was observed on catechol, which is a precursor of semiquinones. On the other hand, semiquinones, radicals usually formed as a result of catechol interaction with red blood cells, are not affected by the action of *U. tomentosa*. However, the ethanolic extracts were more effective than the aqueous ones.

The antioxidant effect of leaf and bark ethanolic extracts from *U. tomentosa* was also detected in mononuclear blood human cells.[44] Moreover, Dal Santo et al.[45] evaluated the protective effect of *U. tomentosa*, in the form of hydroalcoholic extract, on acute exposure to glyphosate-Roundup using zebrafish as a model system. The exposure to the Roundup, a glyphosate-based herbicide, induces a whole series of effects on plants and plant-eating animals, including the onset of OS and genotoxicity. *U. tomentosa* extract was able to avoid oxidative damage induced by Roundup in zebrafish probably because of its ROS scavenger ability. The extract was found to contain essentially phenols and flavonoids which are really effective antioxidant substances.

Cancer and *U. tomentosa*

U. tomentosa has been traditionally used in the treatment of various diseases, including cancer. *U. tomentosa* is one of the best-selling plants in the world and is used as immunomodulatory, anti-inflammatory, and anticancer. For the last couple of decades, researchers have experimented several methods of extraction to study pharmacological properties of the plant with antitumor activities. Antitumor effects of *U. tomentosa* have been shown in vitro and in some animal models. Compounds isolated from *cat's claw* have shown inhibitory activity against different human cancer cell lines, causing increased DNA damage and cell death.

Several reports have shown that *U. tomentosa* extracts and preparations inhibit tumor growth and metastasis in mouse and rat models.[35, 37, 46–50]

In a previous study, Coussens and Werb[51] suggested, in light of the well-established role of chronic inflammation in cancer progression, that the anti-inflammatory activity of *U. tomentosa* may be at least partially responsible for its anti-tumor activity.[37]

The *U. tomentosa* component called mitraphylline demonstrated in vitro antitumoral activity against human neuroblastoma and glioma cell lines.[52] Despite the ineffectiveness of *U. tomentosa* extract in regulating glutathione (GSH) and lipidic peroxidation (LPO) level, it may be suggested that *U. tomentosa* extract is interesting as an adjuvant in the treatment of solid tumors. The fundament of this statement occurs, partially at least, because of its action on enzymes that regulate OS. It is well known that the interference in some redox processes and ROS metabolism are a possible way of achieving apoptosis in neoplastic cells.[53, 54]

Dreifuss et al.[35] showed in vivo the importance of the modulation of OS as part of the antineoplastic activity of *U. tomentosa*, this effect is possibly due to a synergic combination of substances, most of them with antioxidant properties.

Also, Ciani et al.[42] showed that *U. tomentosa* cytotoxicity can be ascribed, at least in part, to its ability both to induce oxidative DNA damage and antagonize the mechanism of DNA repair relying on activity of YB-1, a protein involved in the recognition and repair of DNA lesions. They also showed that squamous carcinoma cells are more susceptible to *U. tomentosa* treatment than untransformed keratinocytes supporting the use of *U. tomentosa* extract for the treatment of precancerous and early forms of squamous cell carcinomas.

Another study investigated the possible proapoptotic mechanism of root bark extracts of *U. tomentosa* in three different tumoral cell lines: SAOS (human osteosarcoma cell line), MCF7 (human breast carcinoma cell line), and HeLa (human cervical carcinoma cell line). Data obtained clearly showed induction of apoptosis, by the *n*-BuOH soluble fraction of *U. tomentosa*, via caspase3 activation.[53]

U. tomentosa methanolic and aqueous extracts were tested against cancer cell lines, in particular against Caco2 (human epithelial colorectal adenocarcinoma cell line) and Hela (human epithelioid cervix carcinoma cell line) cells. The methanolic extract was particularly effective against both cell lines suggesting their potential use in the treatment and prevention of some cancers.[55] In contrast, organic solvent extracts (ethyl acetate, chloroform, and hexane) were less potent in the control of cancer cell proliferation. Moreover, aqueous *U. tomentosa* extract has also been reported to inhibit the proliferation of HL-60 and K562 human leukemia and Raji EBV-transformed B lymphoma cell lines without inducing apoptosis.[56]

U. tomentosa aqueous extract was also demonstrated to be effective against lymphoblastic and breast cancer cell lines by inducing apoptosis.[57, 58] Similarly, apoptotic activity was reported for several *U. tomentosa* hydro-alcohol extracts against human HT-29 and SW707 (colon adenocarcinoma), KB (cervical carcinoma), MCF7 (breast carcinoma), A549 (nonsmall cell lung carcinoma), HL-60 (promyelocytic leukemia) cells, as well as mouse LL/2 (lung carcinoma) and B16 (melanoma) cells.[50]

Chemotherapy is often the recommended treatment for cancer, alone or in combination with other drugs and/or radiotherapy. A frequent consequence of chemotherapy is the appearance of undesirable side effects, including OS. Complementary and alternative medicine is a tool to eventually ameliorate and reduce chemotherapy discomfort.

Breast cancer is the most frequent neoplasm affecting women worldwide. Some of the recommended treatments involve chemotherapy whose toxic effects include leukopenia and neutropenia. *U. tomentosa* has been used to counteract the adverse effects of chemotherapy in a randomized clinical trial. *U. tomentosa* reduced the neutropenia caused by chemotherapy and was also able to restore cellular DNA damage.[59] A similar study demonstrated the effectiveness of *U. tomentosa* in minimizing the side effects of chemotherapy in patients affected by colorectal cancer.[48]

Farias et al.[47] demonstrated that *U. tomentosa*, in mice, had a positive effect on the number of myeloid progenitors and this result is promising for the utilization of the plant extract associated with chemotherapy, with the aim to minimize the side effects of this treatment. Remarkably, *U. tomentosa* has shown a positive effect on myeloid progenitor cells and was suggested as a promising therapy to minimize the adverse effects of chemotherapy.[47]

Antioxidant and antitumoral activities of *U. tomentosa* were demonstrated by Dreifuss et al.[46] in a study performed on a solid tumor. In this experimental study, Walker 256 cells, deriving from rat breast carcinoma cell line syngeneic to Wistar rats, were subcutaneously inoculated in male Wistar rats. The authors revealed a dose-dependent role of *U. tomentosa* hydroalcoholic extract in the reduction of tumor mass and volume and an adjuvant of redox state in the treatment of solid tumors. Both effects are supposed to be due to a noteworthy correlation between the antitumoral properties of *U. tomentosa* and its potential as a free radical scavenger and as a guarantor of ROS homeostasis.

A series of clinical trials have been performed on people affected by various forms of cancer to assess whether *U. tomentosa*, in various forms, could mitigate side effects of chemotherapy. On the basis of these findings, colorectal cancer (CRC) patients were administered *U. tomentosa* in herbal preparation form, corresponding to aqueous extracts, during the chemotherapy treatment. The results showed no significant reduction in the adverse effects of chemotherapy. The authors ascribed this negative result to colectomy, which patients underwent, as the reason why *U. tomentosa* was not adequately absorbed. However, further studies are needed to understand the real reasons for these unsatisfactory results.[48]

Conclusions

The studies on *U. tomentosa* have been conducted using extracts obtained from bark, root or leaves of the plant with aqueous or alcoholic extraction methods. Scientific studies attribute to the extracts of this plant favorable antioxidant and anticancer activities. The chemical analyses of the extracts show the presence of numerous substances, including tannins and phenolic compounds, which act as antioxidants, and alkaloids, in particular the pentacyclic oxindoles, which are considered responsible for numerous anticancer effects in experiments performed on cell cultures and in clinical trials. The combined antineoplastic and antioxidant actions of *U. tomentosa* are indeed promising for its use as therapeutic alone or in combination with other drugs, however, further studies are necessary to improve and standardize the pharmaceutical preparations.

Summary points

- This chapter focuses on *U. tomentosa*, which is a thorny liana that grows wild in the upper Amazon region of Peru and neighboring countries.
- The root and bark extracts have traditionally been used by indigenous people of South America to treat various diseases.
- Many active compounds have been isolated from *U. tomentosa* and extensively studied for their potential use as antioxidant and anticancer agents.
- The chemical analyses of the extracts show the presence of tannins and phenolic compounds, which act as antioxidants, and alkaloids, which are considered responsible for numerous anticancer effects.
- The combined antineoplastic and antioxidant actions of *U. tomentosa* are indeed promising for its use as therapeutic alone or in combination with other drugs.

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