Review Article

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Vilcacora [Uncaria tomentosa (Willd.) DC. and Uncaria guianensis (Aublet) Gmell.] – a review of published scientific literature

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SUMMARY

Uncaria tomentosa (Willdenow ex Roemer and Schultes) DC. and its relative Uncaria guianensis (Aublet) Gmell., both from the Rubiaceae family, are vines growing in jungles of South and Central America. They are widely used in folk and complementary medicine under traditional names: 'Vilcacora', 'una de gato', 'cat's claw', 'cat's crew', 'saventaro', 'hawk's claw', 'samento', 'garabato amarillo' and 'Katzenkralle'. In the genus Uncaria there are also other plants with well-known healing properties, eg. Uncaria rhynchophylla and Uncaria sinensis, one of the most interesting medicinal plants of Asia, similar to Uncaria macrophylla and Uncaria formosana. Vilcacora and its components are of interest to various scientists (physicians, pharmacologists, botanists, and economists) due to their pharmacological properties, as well as ecologic and economic significance. In the reviewed scientific literature more than 45 papers on Vilcacora (chemical constitution, extracts' standardization and quality control, toxicology and pharmacology of crude extracts – experiments in vitro or animal or human experiments in vivo) were published. Scientific literature on active substances present in Vilcacora includes more than a few thousand papers. In this paper, the most significant data on Vilcacora are reviewed, excluding case-reports and other data not confirmed in scientific literature (eg. single patients' or physicians' relations, popular science articles, manufacturers' publications etc.). Only papers published in peer-reviewed scientific journals, indexed in the databases: 'Index Medicus (Medline)', 'EMBASE – Drugs and Pharmacology', 'Chemical Abstracts', 'Biological Abstracts' and 'Review on Medicinal and Aromatic Plants' were covered.

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BACKGROUND

Uncaria tomentosa (Willdenow ex Roemer and Schultes) DC. and its relative *Uncaria guianensis* (Aublet) Gmell, both representatives of the *Rubiaceae* family, are thorny vines naturally occurring in jungles of South and Central America (Peru, Columba, Ecuador, Guiana Venezuela, Trinidad, Surinam, Guatemala, Costarica, Panama). They are widely used in phytoterapy under the names of 'Vilcacora', 'una de gato', 'samento', 'garabato amarillo'; in the United States and Western Europe they are known as 'cat's claw', 'cat's crew', 'hawk's claw' or 'saventaro', in Austria and Germany as 'Katzenkralle', and also under several ten other names. Below they will be collectively referred to as Vilcacora. These species and *Uncaria tomentosa* in particular have interesting botanical history, without the knowledge of it some important information is overlooked. *Uncaria guianensis* was the first species of the genus *Uncaria*, described in 1775 by Aublet as *Ourouparia guianensis*. In 1789, Schreber called this species *Uncaria guianensis* and although the species of the genus *Uncaria* were also classified as belonging to the genus *Nauclea*, the generic name of *Uncaria* is currently regarded as correct [1,2]. The plant now identified as *Uncaria tomentosa* was previously (according to various taxonomic systems) [1–3] referred to by botanists as:

- *Nauclea aculeata* auct. non Willd.
- *Nauclea cinchoneae* DC.
- *Nauclea polycephala* A. Rich.
- *Nauclea tomentosa* Willd.
- *Ourouparia polycephala* Baillon.
- *Uncaria surinamensis* Miq.
- *Uncaria tomentosa* DC.
- *Uruparia tomentosa* O. Kuntze.

Other species of the genus *Uncaria*, known for their medicinal properties, include e.g. *Uncaria rhynchophylla* (closely related to *Uncaria tomentosa*) [4,5] and Uncaria sinensis, one of the most interesting medicinal plants in Asia, like Asian species *Uncaria macrophylla* and *Uncaria formosana*.

Vilcacora and its components have been for many years the object of interest of investigators of various specialties: physicians, pharmacists, botanists, economists. Over 45 papers on Vilcacora – its chemical composition, quality control and standardization of preparations and their toxicology, pharmacological studies of plant extracts without isolation of active substances carried out: *in vitro*, on animals and humans). Scientific bibliography of active substances present in Vilcacora amounts to several thousand publications (in the 'Index Medicus (MEDLINE) only' ca. 120 reports concerning alkaloids present in Vilcacora can be found). Also some review papers and pharmacological monographs concerning Vilcacora and its therapeutic applications have been published [6–10], as well as over ten doctoral and habilitation theses (mainly coming from South America, Germany and Austria) and over ten popular publications. *Uncaria tomentosa* is included among the WHO Medicinal Plants Monographs [11], in British Herbal Pharmacopeia [12], American Herbal Pharmacopeia [13], and as a monographic entry in the latest edition of one of the most important European pharmacopeias: Hagers Handbuch der Pharmazeutischen Praxis [3]. The paper reviews the most important published data concerning Vilcacora, excluding single case reports and information not confirmed by peer-reviewed scientific literature (e.g. patients' and doctors' relations, popular publications and manufacturers' brochures, etc.). It should be emphasized here that besides the above publications, there are numerous *in vitro* and *in vivo* studies (toxicological and therapeutic experiments on animals and clinical trials on humans) carried out e.g. for the purposes of registration of the Vilcacora preparations in various countries or presented only in the form of congress materials, whose results (although known and available) have not been published yet in peer-reviewed scientific publications, so they are not quoted in the present paper.

CHEMICAL COMPOSITION, QUALITY CONTROL AND STANDARDIZATION OF VILCACORA PREPARATIONS

The most important group of biologically active components of Vilcacora are numerous alkaloids, compounds with well-established position among medicinal substances of herbal origin. Alkaloids have (with some exceptions) alkaline character and varied potency of physiological effects. Their molecular structure contains a ring with a nitrogen atom present due to transformation of an amino acid or related compound [14]. Alkaloids are rarely neutral for humans – they may be both potent drugs and lethal poisons [14]. In comparison with other plant species, including those of the genus *Uncaria* Vilcacora contains them in unusual abundance. Two groups of alkaloids are represented in the plant (Table 1): indole alkaloids (hirsutine and hirsutine *N*-oxide, hirsuteine, cory-

Table 1. Alkaloids identified in *U. tomentosa* and *U. guianensis*.

	Indole alkaloids	Oxindole alkaloids
Tetracyclic	Hirsutine and its ***N***-oxide hirsuteine corynantheine dihydrocorynantheine and its ***N***-oxide	rynchophylline and its ***N***-oxide iso rynchophylline and its ***N***-oxide Corynoxeine isocorynoxeine rotundifoline isorotundifoline
Pentacyclic	akuammigine tetrahydroalstonine izoajmalicine Angustine angustoline	pteropodine (uncarine C) isopteropodine (uncarine E) mitraphylline isomitraphylline speciophylline (uncarine D) uncarine F

nantheine, dihydrocorynantheine and dihydrocorynantheine *N*-oxide, akuammigine, tetrahydroalstonine, isoajmalicine; the isolation of angustine and angustoline has also been reported [1]) [1,5,15–19] as well as oxindole alkaloids (rynchophylline and rynchophylline *N*-oxide, isorynchophylline and isorynchophylline hirsutine *N*-oxide, pteropodine or uncarine C, isopteropodine or uncarine E, mitraphylline, isomitraphylline, corynoxeine, isocorynoxeine, speciophylline or uncarine D, uncarine F}; the isolation of rotundifoline, isorotundifoline [1,16] and precursor 5α-carboxystrictosidine has also been reported [20]) [5,19,21–30]. Both groups can be divided in turn into tetracyclic alkaloids (indole: hirsutine, hirsuteine, corynantheine, dihydrocorynantheine; oxindole: rynchophylline, iorynchophylline, corynoxeine, isocorynoxeine, rotundifoline, isorotundifoline), and pentacyclic (indole: akuammigine, tetrahydroalstonine, isoajmalicine, angustine, angustoline; oxindole: pteropodine, isopteropodine, mitraphylline, isomitraphylline, speciophylline, uncarine F) (Table 1). A very important characteristic feature of Vilcacora and other plants of the genus *Uncaria* is a considerable differentiation of individual alkaloid contents in different parts of the plant – the highest in the roots and bark (however, in view of continuous decrease of the plant population, damage and export of roots are prohibited). Moreover, the content of active substances is dependent on the season and geographical location of the site. For these reasons, Vilcacora has to be collected at appropriate time and place and it cannot be cultured for pharmaceutical purposes outside particular areas of South America.

The total content of oxindole alkaloids in extracts made of various harvests of Vilcacora amounts to ca. 6 mg/g raw material [31]. Total alkaloid content in the roots changes according to the season [32,33], with the changes of even forty- to seventy-fold range in various periods of the year [32].

The morphological methods of identification of particular plant species of the genus *Uncaria* are sufficient to determine their identity in natural habitats and in culture [34,35]. However, it has been acknowledged only during the last few years that two chemotypes of *U. tomentosa* species (irrespective of the color varieties), differing considerably in the contents of individual alkaloids and their proportions, can be found in nature [5–8,19]. The first of them, containing predominantly pentacyclic oxindole alkaloids, has been called *pentacyclic alkaloid-type*, whereas the second, containing mainly tetracyclic alkaloids, is known as, *tetracyclic alkaloid-type* [5,19]. The determination of the chemotype is of crucial importance in the analysis and processing of the plant with the aim of obtaining a pharmaceutical preparation, because pentacyclic and tetracyclic alkaloids have different mechanisms of activity and can even be antagonistic to each other [5–8]. Thus, without appropriate standardization of Vilcacora preparations no consistency of their properties can be obtained.

The structure of indole and oxindole alkaloids has been extensively investigated using various techniques [27,36–41]. These alkaloids are characterized by rapid isomerization in aqueous solutions, dependent on pH and temperature [25,42], e.g. Pteropodine is partially converted into isopteropodine [32]. Therefore, experiments of up to several hours' duration only allow to determine the activity of individual alkaloids, whereas longer ones analyze the group of alkaloid isomers rather than the original substances (e.g. pentacyclic or tetracyclic oxindole alkaloids) [43]. The kinetics and mechanism of pentacyclic oxindole alkaloids isomerization process have been extensively investigated [25,42].

Standardization procedures carried out in Western Europe with respect to Vilcacora preparations most frequently involve determination of isopteropodine, an alkaloid possessing most potent immunostimulating properties [32]. Isopteropodine is found mainly in roots, and in smaller quantities also in leaves and bark of *U. tomentosa*. Its content in the plant is also season-dependent [32,33]. The alkaloid is also present in a few other species of the *Rubiaceae* family, as well as in sea snails *Nerita albicilla* [36]. The extracts used in Western Europe (e.g. Krallendorn® manufactured by Immodal Pharmaka GmbH) are most frequently standardized so as to obtain oxindole alkaloid concentration of 1.3–1.75%, with ca. 97% of their content accounting for pentacyclic alkaloids.

Table 2. Properties of hirsutine.

Properties of hirsutine	References
Protection of gastrointestinal mucosa, prevention of induced gastric ulcers in mice	[61]
Hypotensive effect in rats	[61,62]
Vasorelaxation in the femoral, cerebral and coronary arteries in dogs similar to that induced by papaverin	[63]
Inhibition of glutamate-induced convulsions in mice	[64]
Blockade of ganglia and induction of local anesthesia	[65,66,67]
Blockade of voltage-dependent cellular calcium channels	[67,68,69]
In vitro inhibition of A type influenza virus replication	[70,71]
Spasmolytic effect on mouse gut	[61]
Blockade of voltage-dependent cellular potassium channels and nicotine receptor	[67]
Blockade of ligand binding to α- and β-adrenergic and 1A and 2 serotoninergic receptors	[72,73]
Negative chronotropic and antiarrhythmic activity	[74]
Antiarrhythmic activity in aconitine-induced arrhythmias in mice and ouabaine-induced arrhythmias in guinea pigs (as potent as that of ajmaline)	[61]
Inhibition of glutamate-induced necrosis of neurocytes	[75]

Besides the aforementioned alkaloids, Vilcacora contains active polyphenols: tannins and procyanidines [21]. The bark of *U. tomentosa* contains ca. 12% procyanidines, whereas in dry extracts their content reaches 48%, some of them demonstrate pharmecological activity, e.g. anti-inflammatory: ((-)-epicatechine, cinchonaines} [14,44]), hypoglycemizing ((-)--epicatechine) [14]. Vilcacora contains both phenolic tannins, including. Kaempherol and dihydrokaempherol [22], and catechin tannins [21].

Among sterols contained in Vilcacora, β-sitosterol (ca. 60%) constitutes the main fraction. Moreover, stigmasterol and campesterol have been isolated [45]. Over ten quinovic acid glycosides with various glycosylation sites have been identified in Vilcacora extracts, [20,46–50], as well as numerous. Triterpenes including oleanolic acid, ursolic acid and its derivatives, and other compounds [20,49,51,52].

The methods of separation and quantitation of individual *U. tomentosa* alkaloids and/or flavonoids in plant extracts using thin layer chromatography (TLC) [7,53], high-performance liquid chromatography (HPLC) [24,32,35,54,55], capillary electrophoresis (CE) [56,57] techniques as well as their combinations: thin layer/gas-liquid chromatography (TLC/GLC) [15–18], gas chromatography/mass spectrometry (GC/MS) [58], supercritical fluid extraction and GC/MS or HPLC/MS analysis have been developed [58]. The TLC [7,53], HPLC [24] CE [56] techniques have been adopted and can be used for quality control of Vilcacora preparations. HPLC can also be used for identification of *Uncaria* species [24,35,54], and even of the plant organ from which the specimen was taken [24,54].

Over two thousand indole and oxindole alkaloids have been isolated to date, mainly coming from the representatives of three families of *Gentianales: Loganiaceae, Apocynaceae* and *Rubiaceae*. Most of them demonstrate certain biological activity and are either being used im medicine or investigated with the aim of developing new drugs [59]. Therefore, numerous synthesis procedures to obtain alkaloids of this type have been developed [59], including total synthesis of isopteropodine and pteropodine [60] as well as several alternative methods of hirsutine, hirsuteine and tetrahydroalstonine synthesis.

BIOLOGICAL PROPERTIES OF SUBSTANCES FOUND IN VILCACORA

Indole alkaloids

Hirsutine, hirsuteine, corynantheine and dihydrocorynantheine (tetracyclic indole alkaloids) demonstrate similar properties. Hirsutine has been investigated most extensively (Tab. 2). It is a potent antiviral agent, smooth muscle relaxant, thus reducing blood pressure, antispasmodic, gastrointestinal mucosa protector, exhibiting also antiarrhythmic, anticonvulsant and analgesic effects.

Hirsuteine inhibits, in a dose-dependent manner, glutamate-induced convulsions in mice [76] and neurocyte necrosis [75]. It is currently being tested as an antiepileptic agent. It causes non-competitive inhibition of dopamine as a result of nicotine receptor activation in rat pheochromocytomal cells [76] and reduces intracellular concentrations of calcium ions by inhibiting their release from the cellular reserves and inflow from the extracellular compartment [69]. This

is probably the mechanism of its hypotensive effect on rats [62]. The compound exhibits antiarrhythmic activity as well [74]. It induces vasorelaxation in canine arteries, but its effect is less pronounced than that induced by papaverin [63]. It also exhibits *in vitro* inhibition of A type influenza virus replication [71].

Both corynantheine and dihydrocorynantheine are potent and selective inhibitors, partially agonistic to serotonine (5-hydroxytryptamine) [77]. Additionally, dihydrocorynantheine demonstrates mild spasmolytic effect on mouse gut [61] and hypotensive effect in rats [61,78], blocks selectively α1-adrenergic receptors [79] and is an antiarrhythmic agent [74].

Akuammigine blocks α1- and α2-adrenergic receptors (with low selectivity) [80,81], whereas tetrahydroalstonine blocks predominantly α2-adrenergic receptors and demonstrates hypotensive effect [81–84].

Oxindole alkaloids

Generally it can be stated, on the basis of numerous both *in vitro* and *in vivo* studies, thet pentacyclic oxindole alkaloids exert their effect, directly or indirectly, mainly on immune cells, particularly those responsible for nonspecific and cellular immunity [5–8]. Tetracyclic oxindole alkaloids act predominantly in the nervous system, both central and peripheral, and the results of recent studies indicate that their effect on the other systems may be antagonistic to that of pentacyclic alkaloids [5–8,85].

Pentacyclic oxindole alkaloids stimulate vascular endothelial cells to produce hitherto unknown factors activating and regulating proliferation of normal inactive B and T lymphocytes in humans [43], thus normalizing the percentage proportions of lymphocyte fractions without significant changes of total lymphocyte counts per volume unit [5]. The same pentacyclic alkaloids inhibit the proliferation of normal human lymphoblasts and human lymphoblastoma B (Raji) and T (Jurkat) cell lines, without exerting cytotoxic effects [43]. This activity can be inhibited by tetracyclic alkaloids [43].

Pentacyclic oxindole alkaloids found in *U. tomentosa* (except for mitraphylline) exhibit antiproliferative effect on HL60 and U-937 leukemic cell lines, without inhibiting the growth of normal human blood progenitor cells. The most potent activity of this kind has been demonstrated by uncarine F, with IC_{50} = 21.7–29 μmol/l. The mechanism of this effect may involve inhibition of DNA polymerase activity exhibited by *U. Tomentosa* extracts in *in vitro* studies [10,86]. Low concentrations of oxindole alkaloids do not demonstrate potent cytotoxic effects on other tumor cells [21].

Isomitraphylline, isopteropodine, isorynchophylline and pteropodine enhance the activity of phagocytes both *in vitro* and *in vivo* [23].

The properties of rynchophylline and isorynchophylline are very similar and the latter undergoes rapid transformation into the former in acid medium [87]. Both induce hypotensive effect in animal experiments [61,88–90]. Additionally, rynchophylline administered to rats together with dihydralazine inhibits tachycardia developed in response to hypotension [91]. Rynchophylline and isorynchophylline are vasodilators [90] and act as spasmolytics in the mouse gut [61]. Rynchophylline stimulates uterine contractions [29] and is an antipyretic and anti-inflammatory agent [92], additionally enhancing respiratory activity [90]. Rynchophylline blocks voltage-dependent calcium channels with the activity similar to that of verapamil [93–95], acts as an antiarrhythmic agent, blocks voltage-dependent potassium channels [96]. Inhibits neurocyte necrosis induced by glutamate [75], depresses locomotor activity in mice enhancing the sedative and hypnotic effect of pentobarbital, probably by interaction with the central dopaminergic and serotoninergic system [97], finally, exhibits an inhibitory effect on platelet aggregation and thrombosis [98,99]. Isorynchophylline blocks the ganglia [65], depresses locomotor activity in mice like rynchophylline [85], blocks voltage-dependent calcium channels [93,95], induces bradycardia by acting on the sinus node and decelerating atrioventricular conduction; this effect can be inhibited by isoprenaline, but not by atropine [100,101]. Additionally, isorynchophylline inhibits automatism and contractility of isolated guinea pig atria [102] and glutamate-induced neurocyte necrosis [75].

Mitraphylline induces diuresis [103]. Corynoxeine blocks calcium channels with similar potency to that of verapamil [93]. Isocorynoxeine exerts a similar effect [93], additionally inhibiting glutamate-induced neurocyte necrosis [75].

Pteropodine and isopteropodine (uncarines C and E) exhibit weak but consistent cytotoxic effect on mouse fibroblasts and tumor cell lines – human (non-microcellular lung cell carcinoma, cervical carcinoma, prostate carcinoma) and mouse (reticular lymphosarcoma, stomach carcinoma); these alkaloids may also inhibit topoizomerase I [26].

Uncaria elliptica, Uncaria perrottetii (A. Rich.) Merr, *Uncaria homomalla* (Miq.), *Uncaria longiflora* (Poir.) Merr, *Uncaria gambir* (Hunt.) Roxb. And other species of this genus are used as the sources of preparations with various pharmacological activities ranging from antiseptic and astringent to contraceptive. In Asia (Japana, China, Taiwan), intensive studies of i. a. *Uncaria rhynchophylla* (Miq.) Jackson, *Uncaria macrophylla, Uncaria sinensis* (Oliv.) Havil. and *Uncaria formosana* are carried out, first of all because of their hypotensive and anticonvulsant – antiepileptic activity (resulting, among others, from high indole and tetracyclic oxindole alkaloid content, especially that of rynchophylline and isorynchophylline) [104–111]. Antiepileptic effect of *Uncaria rhynchophylla* results probably also from its ability to inhibit lipid peroxidation [111].

Other compounds

Some glycosides, including quinolic acid ones and triterpenea isolated from *U. tomentosa* extracts are antiviral compounds with predominant abti-rhinoviral and anti-VSV (vesicular stomatitis virus) activity [46,48], which also demonstrate anti-inflammatory effect [20].

Triterpenes: ursoloic and oleanolic acid have antioxidative properties [112]. Ursolic acid blocks in over 60% ligand binding to muscarinic receptors [72,73]. It also has antiproliferative activity and induces apoptosis in human: A549 (lung carcinoma), SK-OV-3 (ovarian carcinoma), SK-MEL-2 (skin cancer), XF498 (brain tumor), HCT-15 (colon cancer), SNU-1 (stomach cancer) as well as mouse tumor cell lines: L1210 (leukemia), B16-F-0 (malignant melanoma) [113]. Ursolic acid is present in many plants, has been extensively described in literature and demonstrated to possess numerous pharmacological activities: antiinflammatory (more potent than that of indometacin), antiviral (including antiretroviral IC_{50} = 2.0–18.0 μg/ml), anti-leishmaniosis, antitumor, cytostatic, hypoglycemizing, anticholestatic, antihistaminic, hepatoprotective, diuretic, antiulcer, immunomodulating and immunostimulating, sedative and others. Ursolic acid is also a potent inhibitor of aflatoxin-induced mutagenesis [114]. Oleanolic acid also occurs in many plants, has similarly extensive literature and numerous proven medicinal properties: anti-inflammatory, antiviral (including antiretroviral, IC_{50} = 1.7–21.8 μg/ml), antiatherosclerotic, antibacterial, antimalarial, anti-leishmaniosis, antitumor, hepatoprotective, diuretic, antiulcer, immunomodulating, immunostimulating and others.

Sterols present in *U. tomentosa* are characterized by moderate anti-inflammatory effect [45]. Beta-sitosterol is one of the main soy anticancerogens [114]. Stigmasterol and campesterol demonstrate antiatherosclerotic activity [114].

Polyphenols found in Vilcacora include numerous compounds demonstrating pharmacological activity, e.g. anti-inflammatory ((-)-epicatechine, cinchonaines [14,44]; hypoglycemizing (-)-epicatechine) [14]; as well as dimeric procyanidines with recognized antitumor activity [21,115]. Generally flavonoids, including catechinic tannins, are known as components of beverages (mainly tea), demonstrating anticarcinogenic properties [116], which has been confirmed by numerous epidemiological studies. Water-soluble flavonoids-procyanidines – act as vasoprotectors and anti-inflammatory agents, as well as potent antioxidants. Catechinic tannins are antioxidants protecting i. a. ascorbic acid (Vitamin C) from oxidation [117]. Cis-epicatechine [21] is a particularly potent antioxidant (more than vitamin E) and vasoprotector, prolonging the survival of experimental rats with spontaneous hypertension, susceptible to intracerebral hemorrhages [118]. Tannins and other flavonoids demonstrate positive results on intestinal and bile duct peristalsis, as well as appetite-enhancing effect in many subjects. Galic acid is also an active antitumor compound [114].

Hyperine, also present in Vilcacora, is an antioxidant [114].

Uncarinic acid and pentacyclic triterpene esters isolated from Asian *U. rhynchophylla* are Cγ1 phospholipase (PLCγ1, inhibition constants IC_{50} within the 9.5–44 micromole/dm^3) and human tumor cell inhibitors (inhibition constants IC_{50} within the 0.5–6.5 μg/dm^3 range) [119].

Analyses of *U. tomentosa* extracts without isolation of active substances: *in vitro* experiments, animal studies and clinical trials

One of the most important European pharmacopeias, Hagers Handbuch der Pharmazeutischen Praxis [3], classifies the *U. tomentosa* extract, on the basis of published results, as a preparation possessing the following properties:
– cytostatic,
– contraceptive,
– phagocytosis-stimulating,
– antiviral,
– antiedemal,
– antimutagenic,
– regulating the activity of the CNS.

The most important findings concerning Vilcacora extracts are summarized below.

C-MED-100™ - aqueous *U. tomentosa* extract with reduced indole alkaloid content induces delayed type apoptosis and inhibits in a concentration-dependent manner *in vitro* proliferation of human tumor cells: leukemic HL60 and EBV-transformed B cell (Raji) lymphoma cell line [120]. The K562 leukemic cell lines are less susceptible to the effect of the extract [120]. The same extract administered to rats *in vivo* increases leukocytosis and stimulates *in vitro* proliferation of isolated rat lymphocytes; similarly, it enhances leukocytosis in healthy volunteers [121]. C-MED-100™ administered to rats *in vivo* enhances the cellular repair potential with respect to damages of one and both DNA strands due to whole body irradiation delivered in 12 Gy dose [121]. Its therapeutic effect in rats with doxorubicin-induced leukopenia involves effective normalization of leukocyte paramaters, better than after filgrastim routinely used for this purpose (filgrastin therapy results mainly in an increase of the neutrophil fraction, whereas *U. tomentosa* extract normalizes lekocytosis in all fractions) [122]. The above could provide a partial explanation of the positive results of *U. tomentosa* extracts administered as adjuvants during chemo- or radiothrapy.

In *in vitro* studies, aqueous Vilcacora extracts specifically and non-competitively blocks the binding sites of estrogen receptors with effectiveness similar to that of tamoxifen [123].

In HIV-positive patients with reduced lymphocyte counts, Vilcacora administered for 2.2–5.0 months increased the number of these blood cells [5].

Aqueous extracts of *U. tomentosa* exhibit potent immunostimulating effect by stimulating alveolar macrophages in lungs to produce interleukin-1 and interleukin-6 in a dose-dependent manner within the 0.025–0.1 mg/ml range of oxindole alkaloid concentrations [31].

U. tomentosa extract stimulates primary immune response and delayed hypersensitivity type reaction against sheep erythrocytes in mice, inhibiting at the same time pseudoallergic inflammatoty process [124].

Aqueous Vilcacora extract is a potent cytoprotector with respect to macrophages and human epithelial cell lines exposed to the factors inducing *in vitro* apoptosis by induction of oxidative stress in these cells [125,126]. At the same time, the extract demonstrates *in vitro* potent anti-inflammatory activity, inhibiting the activation of the NF-κB transcriptional factor and induction of genes inducible under inflammatory conditions, specifically inducible nitrogen oxide synthetase and production of nitrites in human epithelial cells and mouse macrophagic line [125]. Moreover, the extract causes potent inhibition of tumor necrosis factor (TNFα), which is probably the main mechanism responsible for anti-inflammatory effect of *Uncaria* [126]. Non-fractioned aqueous Vilcacora extracts also exhibit anti-inflammatory effect in the test of carragenine-induced edema inhibition in rats [20].

Under in vivo conditions, aqueous *U. tomentosa* extract administered *per os* to Sprague-Dawley rats at doses calculated proportionally to those routinely used in humans significantly protects the intestinal mucosa from indometacin-induced damage [125]. It inhibits there indometacin-induced synthesis of hepatic metallothioneins, the level of which is a marker of hepatitis. The above confirms the potent anti-inflammatory *in vivo* effect of Vilcacora extract [125].

Alcohol extracts of *U. tomentosa* cause potent inhibition of cytochrome P450 3A4 (CYP3A4) *in vitro* activity, which suggests the necessity of studies concerned with interactions of such extracts with the metabolism of drugs and other xenobiotics undergoing biotransformation by the microsomal system [127].

Methanol extracts from various parts of *U. tomentosa* prevent generation of free radicals and lipid peroxidation under *in vitro* conditions (in rat liver homogenates), with the effect reaching significance at IC_{50} = 56–259 μg/ml, inhibit the damaging effect of free radicals on saccharide elements of DNA [128,129] and cell necrosis due to free radical activity [126]. Antioxidative properties of *U. Tomentosa* extracts are more potent in the lipid phase than in the aqueous one [130]. In humans (both healthy subjects and diabetics) these extracts effectively inhibit synthesis of free radicals by peripheral blood neutrophils [131]. Similar antioxidative properties have been observed with respect to *Uncaria rhynchophylla*, commonly used in Chinese medicine [131,132]. Asian species of *Uncaria* are believed to protect arteries from hypertension-related damage [133]. Moreover, they are effective hypotensive agents, [134], particularly active with respect to regulation of blood flow in the CNS, preventing hemorrhagic and ischemic strokes in hypertensive subjects [135].

Extracts from the plant and chromatographic fractions from *U. tomentosa* stalk extract separation exhibit antimutagenic effect on *Salmonella typhimurium*

subjected to 8-methoxy-psoralene-induced or UV-A--induced photomutagenesis [136]. *U. tomentosa* extract taken by a smoker for the period of 15 days led to a significant reduction of mutagenic activity in his urine in the same test. No such effect was observed in a non-smoker receiving the extract [136].

Toxicology and safety of treatment. Safe and routine doses.

Aqueous *Uncaria tomentosa* extract even administered at high doses did not cause acute toxic symptoms in mice (with the LD_{50} value for mice presumed as >16 g/kg b.w.). In rats, LD_{50} exceeds 8 g/kg b.w. [121]. Administration of 160 mg/kg doses for 4 weeks or 10–80 mg/kg doses for 8 weeks did not cause acute or chronic toxic symptoms or organic lesions in these animals [121]. Aqueous *U. tomentosa* extract administered to rats for 4 weeks caused only moderate lymphocytosis [5,43].

Patent-related literature contains the results of studies concerning acute toxicity of aqueous *Uncaria tomentosa*, extract, which administered to mice at doses up to 5 g dry mass per kg body weight did not cause nay toxic symptoms [116].

Extracts from the plant and chromatographic fractions from *U. tomentosa* stalk extract separation did not demonstrate mutagenic effects in tests in *Salmonella typhimurium* [136].

In tests carried out on healthy volunteers, aqueous extract of *U. tomentosa* C-MED-100™ administered for 6 weeks at 5 mg/kg b.w. doses did not cause toxic symptoms, inducing at the same time a statistically significant increase of leukocytosis [121]. Also in other volunteers taking *U. tomentosa* extracts no toxic symptoms due to the treatment were noted [136].

In *in vitro* studies carried out on hamster ovary cells (CHO) and *Photobacterium phosphoreum* cultures in four cytotoxicity control systems, aqueous *U. tomentosa* extract did not demonstrate the presence of substances toxic to the test cells [137].

Although Vilcacora extracts exhibit no detectable toxicity even in high doses, some isolated components of the plant may be toxic at higher concentrations [138].

In Western Europe, *U. tomentosa* extracts are used at ca. 20–60 mg dry extract daily doses. Pentacyclic oxindole alkaloids are poorly soluble in water and well in acids and alcohols, so *U. tomentosa* extracts are prepared in the form of 50% water-alcohol tinctures. In Germany and Austria, standardized powdered extract of *U. tomentosa* is used 2–3 times a day in 20–60 mg daily doses.

The dosage of *U. tomentosa* preparations should take into acount the high content of tannins, which, besides their protective activity, are alsoantinutritional agents [139].

Medicinal applications and legal status

Research data concerning medicinal applications of Vilcacora are rather scarce, as numerous studies have not been completed yet. Some results are available only as reports from clinical trials prepared by manufacturers within the framework of registration procedures (e.g. a series of studies by Immodal Pharmaca GmbH, Austria). *U. tomentosa* preparations have been qualified for sale and use in many countries (including, i.a. Austria, Russia, Spain, Canada, Germany, Great Britain, Italy, Ukraine), in Poland the registration process is now under way. In the USA Vilcacora is used legally under local regulations concerning 'dietary supplements'. In Austria and Germany, preparations from *U. tomentosa* root are used mainly in immune disorders (including allergies, rheumatoid arthritis) and as adjuvant therapy of malignancies (alleviating the consequences of chemo- and radiotherapy, started generally 2 weeks before the commencement of radio- or chemotherapy course, as well as in patients with poor prognosis not qualified for radical or survival-prolonging therapy, as an adjuvant in viral infections with herpes or retroviruses such as HIV. The preparation is not officially used in children below 3 because of no clinical trials carried out in this age group. It seems that in view of immunostimulating properties of Vilcacora the preparation should not be recommended to patients after transplantations or qualified for these procedures, as well as in pregnancy.

Vilcacora is sold in Poland under various names, although it has not been registered yet by the institute of drugs. As a result, there are no appropriate standards and any possibilities to control the content and quality of available preparations. From the experience of other countries it follows that the preparations sold in the black market may have varied composition and content, and significant falsifications have been observed, especially with respect to non-legalized preparations coming from China and the Andes. The processed and standardized Vilcacora extracts available in European markets include „Krallendorn®" by an Austrian Immodal Pharmaca GmbH

Company (which has undergone preclinical and clinical trials concerning its various applications) [5] and recently introduced C-MED-100™ (Campa Med, New York, USA) the preliminary studies of which have been completed so far [120–122].

Economic aspects

The interest in economic aspects of Vilcacora dates back to the appearance of first reports in scientific journals [140,141]. Under natural conditions, Vilcacora is not very common in the Amazon jungle with the occurrence rate of ca. 2–8 plants per 1 hectare, whereas in man-planted forests the occurrence may increase to ca. 17 plants per 1 hectare [142,143]. The vine stem can be used only after the plant reaches the age of ca. 8 years. The registered global turnover with respect to Vilcacora preparations noted in 1995 reached 3 million dollars and at least 726 t of *Uncaria* were legally exported from Peru [143,144]. Over 50 US companies specializing in sales of so-called dietary supplements include Vilcacora in their offer [5]. Because of limited natural resources, Peru (in the territory of which the most commonly used varieties of *Uncaria tomentosa* are found) has introduced drastic restrictions for the export of raw material and permits export of partially processed material only [144]. Inflicting any damage to the roots, which are the most valuable parts of the plant, is prohibited, so bark is used instead. Attempts to grow Vilcacora in field culture conditions are undertaken, which is a prerequisite for legal export of raw material in future [143].

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