

REVIEW

An Exploration of Phytochemicals from *Simaroubaceae*

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Abstract

Natural products such as plants, animals and minerals have been the basis of treatment of human diseases. Herbal remedies have been used for the treatment of many ailments. Many compounds have been derived from the plant species mentioned in the ancient texts of Indian system of medicine for the treatment of a number of ailments. The R and D thrust in the pharmaceutical sector is focused on development of new drugs, innovative/indigenous processes for known drugs and development of plant based drugs through investigation of leads from the traditional systems of medicine. The family *Simaroubaceae* is grouped in the order Rutales, is known to have a diverse range of secondary metabolites. Plants from this family are used as medicine to cure cancer and many other diseases. Isolation of diverse chemical compounds from *Simaroubaceae* on its stem bark, root bark and leaves have been reported. In this review, we are analysing with the chemical constituents of family *Simaroubaceae*.

Keywords: Simaroubaceae- Quassinoids- Polyphenols

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Introduction

The *Simaroubacea* family includes 32 genera and more than 170 species of trees and bushes of pantropical distribution. It is characterised by its contents of bitter components, mostly responsible for its pharmaceutical properties (Fernando et al., 1995, Muhammad et al., 2004). The main distribution hot spots are located at tropical areas of America, extending to Africa, Madagascar and regions of Australia bathed by Pacific. This family is characterised by the presence of Quassinoids and secondary metabolites responsible for the biological activities.

Simarouba is a medium-sized tree that grows up to 20m high, with a trunk of 50-80cm indiameter. It produces bright green leaves of 20-50cm length, small white flowers and small red fruits. It is indigenous to the Amazon rainforest and other tropical areas in Mexico, Cuba, Haiti, Jamaica, and Central America. The *Simaroubaceae* family has been the subject of many studies regarding its chemical constitution and numerous compounds were isolated and their structure were elucidated, among these quassinoids, alkaloids, triterpenes, steroids, coumarins, anthraquinones, and flavonoids and other metabolites were present. (Barbosa et al., 2011). Quassinoids can be considered as a taxonomic marker of the *Simaroubaceae* family since it is the most abundant group of natural substances and their synthesis almost exclusive (Saraiva et al., 2006, Almeida et al., 2011).

Quassinoids are the main active group of chemicals in Simarouba which belongs to the triterpene chemical family. Several Quassinoids found in Simarouba, such

as ailanthinone, glaucarubinone and holacanthone, are considered the plant's main therapeutic constituents and are the ones documented to be antiprotozoal, anti-amebic, antimalarial and even toxic to cancer and leukemic cells (www.rain-tree.com/simarouba.html).

Quassinoids in simarouba family consist of triterpene degradation products, derived from the euphol/ tirucalol series, highly oxygenated and structurally complex. Regarding the basic structure, they can be structurally classified into five groups: C-18 (1), C-19 (2), C-20 (3), C-22 (4) and C-25 (5a, b), though some do not fit into any given configuration, such as (+)-polyandrol, eurylactones A and B, ailanquassins A and B, 6-dehydroxy-longilactone and others. Most of the isolated quassinoids have a twenty carbon skeleton (Curcino et al., 2006).

The chemical compound Quassia has been used for malaria in the Amazon region. It has been used topically for measles and orally or rectally for intestinal parasites, diarrhea, and fever (Schulz et al., 1998). The first isolated and identified quassinoids were quassin and neoquassin from *Quassia amara* by Nuclear Magnetic Resonance (NMR) (Clark et al., 1937). Two hundred quassinoids were currently isolated and identified (Curcino et al., 2007).

Thirty nine quassinoids were isolated from nine species of the genus *Simaba* (Barbosa et al., 2011). There were reports that ninety one terpenoids were found in eight species of the genus *Ailanthus*, which has been predominantly included quassinoids (Kundu et al., 2004).

A secondary metabolite is a natural product, but a natural product isn't necessarily a secondary metabolite (Bently et al., 1999). Secondary metabolites are

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classified depending on their structural scaffold. These classes include among others polyketides (PKs), non ribosomal peptides (NRPs), terpenoids, alkaloids or hybrid metabolites of the different classes. The function of secondary metabolites in their hosts has not yet been exploited to its fullest; however, they seem to have several functions including defense, communication, and signaling (Calvo et al., 2002, Fox et al., 2008, Kempken et al., 2010, Rohlf et al., 2011).

Although there are notable exceptions (e.g., palytoxin, autotoxin), most secondary metabolites have relative molecular masses less than 1500 Da. The range of chemical structures is breathtaking from simple aliphatic acids (e.g., itaconic acid, C₅H₆O₄) to complex structures such as alkaloids and toxins (e.g., palytoxin, C₁₂₉H₂₂₃N₃O₅₄). This wide range of chemical types has made secondary metabolites a major topic for study by organic chemists (Bentley et al., 1999). Among the alkaloids isolated from the different genera of the Simaroubaceae family, the canthines constitute a class of β -carboline alkaloids. Canthin-6-ones have been reported to have a large array of activities, such as antiviral, cytotoxic, antiparasitic, antibacterial, high pro-inflammatory cytokines reducer, among others (Showalter et al., 2013).

Twenty triterpenes have been reported in six different species of the genus *Simarouba* (Barbosa et al., 2011). There were reports on ninety one terpenoids, which includes quassinoids also (Kundu et al., 2004). This class of secondary metabolites has been largely reported in the literature for numerous genera of *Simaroubaceae*, like *Quassia*, *Brucea*, *Picramnia*, *Castela*, *Simarouba* and *Ailanthus*. (Kundu et al., 2004). Eight steroids were isolated from four species of the genus *Simaba* and their structure was elucidated (Barbosa et al., 2011). The isolation of twenty seven steroids from four species of *Ailanthus* was performed (Kundu et al., 2004).

Polyphenols, anthraquinones, coumarins, flavonoids, lignans, limonoids, quinines, fatty acids, phenylpropanoids and vitamins have been reported for the different species of the *Simaroubaceae* family, although many species have not been chemically studied yet (Iasmine et al., 2014). The vast range of biological activities of the different species of *Simaroubaceae* are given, mainly, due to the quassinoids, for which were attributed antitumor, antimalarial, antiviral, anorectic, insecticide, amebicide, antiparasitic and herbicide activities (Bhattacharjee et al., 2008). Coumarin is a fragrant compound in the benzopyrone chemical class and is a colorless crystalline substance in its standard state. It is found naturally in many plants. Coumarins are used in the pharmaceutical industry as precursor molecules in the synthesis of a number of synthetic anticoagulant pharmaceuticals similar to dicoumarol. Coumarins have shown many biological activities, but are approved for only a few medical uses as pharmaceuticals. Reported coumarin activity includes anti-HIV, anti-tumor, anti-hypertension, anti-arrhythmia, anti-inflammatory, anti-osteoporosis, antiseptic, and analgesic activity. It is also used in the treatment of asthma and lymphedema (Liu et al., 2011). Flavonoids are polyphenolic compounds that are ubiquitous in nature. Over 4,000 flavonoids have

been identified. The wide spread distribution of flavonoids, their variety and their relatively low toxicity compared to other active plant compounds (for instance alkaloids) mean that many animals, including humans, ingest significant quantities in their diet. Preliminary research indicates that flavonoids may modify allergens, viruses, and carcinogens, and so may be biological “response modifiers”. In vitro studies show that flavonoids also have anti-allergic, anti-inflammatory, anti-microbial, anti-cancer, anti diarrheal and antiviral activities (Spencer et al., 2008, Yamamoto et al., 2001, Cushnie et al., 2011, De Sousa et al., 2007, Schuier et al., 2005), Gonzalez et al., 1990).

Medicinal plants produce natural products with a large diversity of chemical structures, which might prove to be suitable for specific medicinal applications.

Most of these secondary metabolites show biological activities in pharmaceutically relevant bioassay systems and thus represent potential lead structures, which could be optimized to yield effective therapeutic and bioactive agents.

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References

- Almeida VC, Filho R, Niero BK, et al (2011). Pharmacological mechanisms underlying the anti-ulcer activity of methanol extract and canthin-6-one of *Simaba ferruginea* A. St-Hil. in animal models. *J Ethnopharmacol*, **134**, 630-6.
- Barbosa R, Braz-Filho I (2011). Vieira Chemical constituents of plants from the genus *Simaba* (Simaroubaceae). *Chem Biodivers*, **8**, 2163–78.
- Bentley R (1999). Secondary metabolite biosynthesis: the first century. *Crit Rev Biotech*, **19**, 1-40.
- Bhattacharjee SG, Gupta P, Bhattacharya A, et al (2008). Quassin alters the immunological patterns of murine macrophages through generation of nitric oxide to exert antileishmanial activity. *J Antimicrob Chemother*, **63**, 317-24.
- Calvo AM, Wilson RA, Bok JW, et al (2002). Relationship between secondary metabolism and fungal development. *Microbiol Mol Biol Rev*, **66**, 447-59.
- Clark EP, Quassin I (1937). The preparation and purification of quassin and neoquassin, with information concerning their molecular formula. *J Am Chem Soc*, **59**, 927–31.
- Curcio V, Braz-Filho R (2006). Quassinoids: structural diversity, biological activity and synthetic studies. *Stud Nat Prod Chem*, **33**, 433–92.
- Cushnie TPT, Lamb AJ (2005). Antimicrobial activity of flavonoids. *Int J Antimicrob Agents*, **26**, 343-56.
- Cushnie TPT, Lamb AJ (2011). Recent advances in understanding the antibacterial properties of flavonoids. *Int J Antimicrob Agents*, **38**, 99-107.
- de Sousa RR, Queiroz KC, Souza AC, et al (2007). Phosphoprotein levels, MAPK activities and NF kappaB expression are affected by fisetin. *J Enzyme Inhib Med Chem*, **22**, 439-44.
- Duke JA (1976). CRC handbook of medicinal Herbs. Boca Raton, FL, CRC Press, 1985. p 399.
- Fernando PA, Gadek CJ (1995). Quassin simaroubaceae: an artificial construct: evidence from rbcL sequence variation.

- Am J Bot*, **82**, 92–100.
- Fox EM, Howlett BJ (2008). Secondary metabolism: regulation and role in fungal biology. *Curr Opin Microbiol*, **11**, 1-7.
- González ME, Martínez-Abarca F, Carrasco L(1990). Flavonoids: Potent inhibitors of poliovirus RNA synthesis. *Antivir Chem Chemother*, **1**, 203-9.
- Iasmine ABSA, Henrique MM, Luiz ALS, Karina PR (2014). Simaroubaceae family: botany, chemical composition and biological activities. *Rev bras farmacogn*, **24**, 481–501.
- Kempken F, Rohlfs M (2010). Fungal secondary metabolite biosynthesis – a chemical defence strategy against antagonistic animals?. *Fungal Ecol*, **3**, 107-14.
- Kundu PC, Damu AG, Lee KH (2004). Cytotoxic and antimalarial constituents from the roots of *Eurycomalongifolia*. *Bioorg Med Chem*, **12**, 537-44.
- Kupchan SM, Strelman DR (1975). Quassimarin, a new antileukemic quassinoid from *Quassia amara*. *J Org Chem* **41**, 3481-2.
- Liu H (2011). Extraction and isolation of compounds from herbal medicines. In: Willow, J. and H. Liu (Eds.) Traditional herbal medicine research methods. John Wiley and Sons, Inc.
- Muhammad E, Bedir SI, Khan R, et al (2004). Walker a new antimalarial quassinoid from *Simarouba orinocensis*. *J Nat Prod*, **62**, 772–7.
- Rohlfs M, Churchill ACL (2011). Fungal secondary metabolites as modulators of interaction with insects and other arthropods. *Fungal Genet Biol*, **48**, 23-34.
- Saraiva RCG, Pinto AC, Nunomura F, et al (2006). Triterpenos e alcaloides tipocantínicos dos galhos de *Simarouba polyphylla* (Cavalcante) W. W. Thomas (Simaroubaceae). *Quim Nova* **29**, 264-8.
- Schuijter M, Sies H, Illek B, et al (2005). Cocoa-related flavonoids inhibit CFTR-mediated chloride transport across T84 human colon epithelia. *J Nutr*, **135**, 2320-5.
- Schulz V, Tyler VE (1998). Rational phytotherapy: A physician's guide to herbal medicine. Berlin: Springer, p 171.
- Showalter HDH (2013). Progress in the synthesis of canthine alkaloids and ring-truncated congeners. *J Nat Prod*, **76**, 455-67.
- Spencer JPE (2008). Flavonoids: modulators of brain function? *Br J Nutr*, **99**, 60-77.
- www.rain-tree.com/simarouba.html.
- Yamamoto Y, Gaynor RB (2001). Therapeutic potential of inhibition of the NF-κB pathway in the treatment of inflammation and cancer. *J Clin Invest*, **107**, 135-42.