Sains Malaysiana 51(3)(2022): 757-774
http://doi.org/10.17576/jsm-2022-5103-10

Phytochemical Constituents and Pharmacological Activities of *Picrasma javanica*: Quassinoids Interest

(Kandungan Fitokimia dan Aktiviti Farmakologi *Picrasma javanica*: Kepentingan Quasinoid)

MUHAMMAD TAHER[1], NAJAH FATEHAH MOHD RAZALI[1], DENY SUSANTI[2,*], MD. ATIAR RAHMAN[3], MUH ADE ARTASASTA[4] & ZAINUL AMIRUDDIN ZAKARIA[5]

[1]*Department of Pharmaceutical Technology, Faculty of Pharmacy, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, 25200 Kuantan, Pahang Darul Makmur, Malaysia*
[2]*Department of Chemistry, Faculty of Science, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, 25200 Kuantan, Pahang Darul Makmur, Malaysia*
[3]*Department of Biochemistry & Molecular Biology, University of Chittagong, Chittagong-4331, Bangladesh*
[4]*Department of Biomedical, Faculty of Medicine, Andalas University, Padang 25163, Indonesia*
[5]*Department of Biomedical Science, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor Darul Ehsan, Malaysia*

Received: 9 July 2020/Accepted: 12 August 2021

ABSTRACT

Picrasma javanica Blume is a plant belonging to Simaroubaceae. It is known for its secondary metabolites, namely quassinoids, offering various pharmacological properties including antitumor, antimalarial, and antiviral. The plant is traditionally used as a source medicine for different diseases in Myanmar, Thailand, and Indonesia. Despite the extensive studies on *P. javanica,* there is no concise and conclusive information regarding the phytochemical and phytochemistry of the plant has been reported. Thus, we aimed to discern the phytochemical constituents and pharmacological activities of *P. javanica.* The phytochemical constituents and pharmacological benefits of *P. javanica* were reviewed and supported from previous *in vivo* and *in vitro* studies. The literature used in this review were retrieved from electronic database such as Scopus, Semanticscholar, Sciendirect, Google scholar, Researchgate, Pubmed, and websites. *P. javanica* possesses several phytochemical constituents, such as quassinoids, alkaloids, and triterpenoids. The compounds of the plant have been isolated and studied for their pharmacological activities, encompassing antimalarial, antiproliferative, antiviral, antimicrobial, and membrane-stabilizing activities. It was found that the pharmacological activities in the plant were attributable to the key ingredients of quassinoids and alkaloids present. However, further extensive studies must be carried out to explore more potential benefits that the plant could offer.

Keywords: Pharmacological activities; phytochemical constituents; *Picrasma javanica;* quassionoids; Simaroubaceae

ABSTRAK

Picrasma javanica Blume ialah sejenis tumbuhan yang tergolong dalam Simaroubaceae. Ia terkenal dengan metabolit sekundernya, iaitu quasinoid yang menawarkan pelbagai sifat farmakologi termasuk antitumor, antimalaria dan antivirus. Tumbuhan ini secara tradisinya digunakan sebagai punca ubat untuk pelbagai penyakit di Myanmar, Thailand dan Indonesia. Walaupun terdapat kajian meluas mengenai *P. javanica*, namun maklumat ringkas dan konklusif mengenai fitokimia dan fitokimia tumbuhan telah dilaporkan. Oleh itu, kami berhasrat untuk membezakan konstituen fitokimia dan aktiviti farmakologi *P. javanica*. Konstituen fitokimia dan faedah farmakologi *P. javanica* telah disemak dan disokong daripada kajian *in vivo* dan *in vitro* sebelum ini. Kepustakaan yang digunakan dalam ulasan ini diperoleh daripada pangkalan data elektronik Scopus, Semanticscholar, Sciendirect, Google scholar, Researchgate, Pubmed dan laman sesawang. *P. javanica* mempunyai beberapa konstituen fitokimia, seperti quasinoid, alkaloid dan triterpenoid. Sebatian tumbuhan telah diasing dan dikaji untuk aktiviti farmakologinya, merangkumi aktiviti antimalaria, antiproliferatif, antivirus, antimikrob dan penstabilan membran. Didapati bahawa aktiviti farmakologi dalam tumbuhan adalah disebabkan oleh bahan-bahan utama quassinoid dan alkaloid yang ada. Walau bagaimanapun, kajian lanjut mesti dijalankan untuk meneroka lebih banyak potensi faedah yang boleh ditawarkan oleh tumbuhan ini.

Kata kunci: Aktiviti farmakologi; juzuk fitokimia; *Picrasma javanica*; quasionoid; Simaroubaceae

Introduction

The use of natural products in medicine has been recorded over many centuries. In fact, this is a long-standing practice throughout history and mankind, especially with the emergence of new diseases and illnesses due to increased global population and ever-changing environments. Natural products such as plants and marine organisms have been utilized, as they are comprised of wide-ranging chemical and structural diversity, as well as various biological activities. The combination of these activities with recent technological advances may position for new drug discoveries if comprehensively investigated for. In light of this notion, the current paper emphasizes on the phytochemistry and pharmacological activities of a specific plant species, namely *P. javanica*.

P. javanica Blume synonym *P. nepalensis* A.W. Bennett or *P. philippinensis* Elmer (Globinmed 2019) is member of the Simaroubaceae plant family, which consists of 32 genera and more than 170 species of plants. *P. javanica* is widely distributed in Myanmar and throughout southeastern Asia as far as the Solomon Island as shown in Figure 1 (www.gbif.org/species/3708935).

P. javanica is a medium-sized tree that may grow

FIGURE 1. Distribution of *P. javanica* Blume (www.gbif.org)

up to a height of 25 m and commonly found in north eastern India and throughout South East Asia. It is often characterized by its bitterness, which is attributed to the presence of quassinoids as any other plants in the Simaroubaceae family (Globinmed 2019). The plant is traditionally used in countries like Myanmar, Thailand, and Indonesia as a medication for malaria, cancer, and acquired immune deficiency syndrome (AIDS) (Win et al. 2015). It also reduces fever and serves as a replacement of quinine (Bora et al. 2007; Globinmed - *Picrasma javanica* Blume; Win et al. 2015).

The traditional use of *P. javanica* as medicine for disease treatment has allocated researchers to initiate studies regarding its activities, especially due to the plant and other members of the family that are yet to be extensively studied. This is in addition to the Simaroubaceae family that is already known for their potential as a source of bioactive molecules and possessing curative properties beneficial to mankind. With this in mind, the present paper intended to focus

on the phytochemical and pharmacological properties of *P. javanica* and subsequently direct future studies and exploitations regarding the values attributed to the plant.

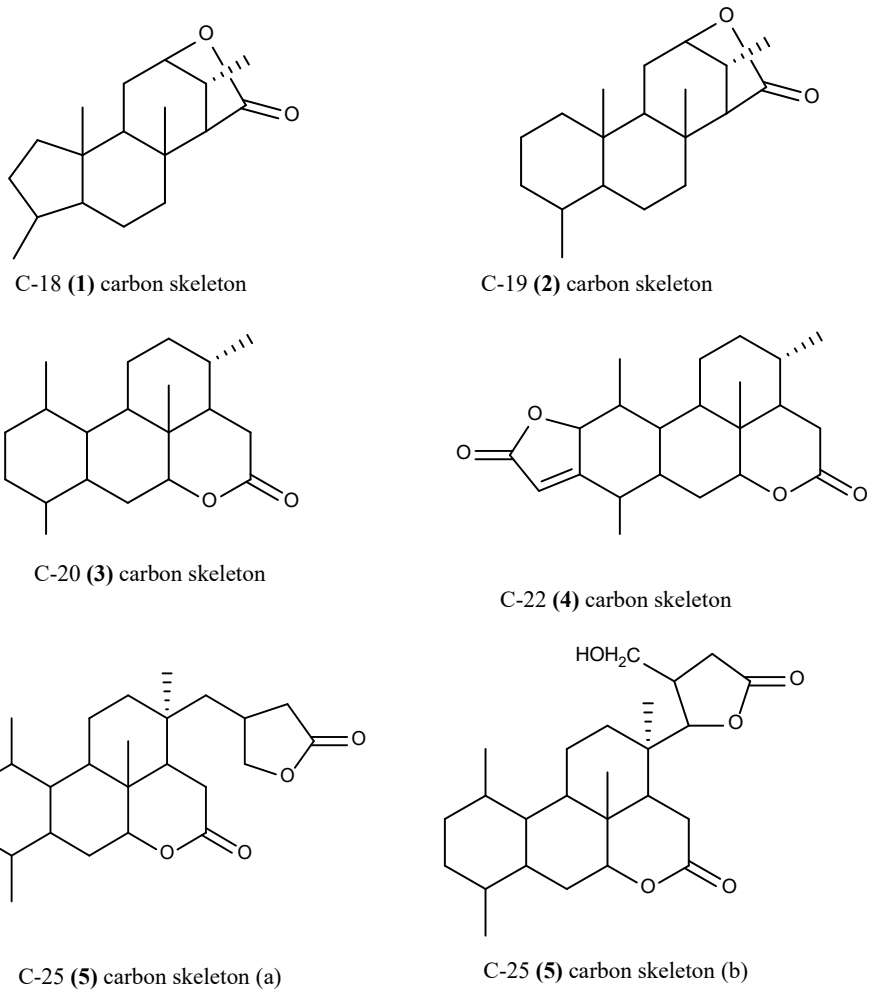
Methods

This paper highlighted the phytochemical constituents and pharmacological activities of previously studied *Picrasma javanica*. The keywords used in searching the references were 'Simaroubaceae'; '*Picrasma javanica'*; 'quassionoids'; 'phytochemical'; 'pharmacological properties'; 'antimalarial'; 'anti-proliferative activity'; 'antiviral'; 'antibacterial'; and 'membrane-stabilizing activity' from electronic database Scopus, Semanticscholar, Sciendirect, Google scholar, Researchgate, Pubmed, and websites.

Phytochemical constituents

Simaroubaceae consists of plants with a multitude of recognized individual compounds, mainly quassinoids, alkaloids, triterpenes, steroids, as well as other different classes. Researchers have previously underlined quassinoids as the most abundant group of compounds in this particular family (Alves et al. 2014; Win et al. 2015). These groups of compounds may either be in the free state or in the form of esters, which are all chemically related (Polonsky 1973). In fact, the bitterness often associated to the plant family of Simaroubaceae is due to the presence of quassinoids (Curcino Vieira & Braz-Felho 2006). The group of compounds can be classified into five distinct groups according to their basic skeletons, namely: groups C-18 **(1)**; C-19 **(2)**; C-20 **(3)**; C-22 **(4);** and C-25 **(5)** (Alves et al. 2014; Curcino Vieira & Braz-Felho 2006; Polonsky 1973). Compounds **1-5** in Figure 2 demonstrate the carbon skeleton structure of quassinoids.

P. javanica is found to have many phytochemical constituents isolated from varying and different parts of the tree, which include the stem, leaves, bark, and fruits. These compounds have been obtained and identified by numerous analytical methods, such as Nuclear Magnetic Resonance (NMR) Spectroscopy, Infrared (IR) Spectroscopy, High Performance Liquid Chromatography (HPLC), and Ultraviolet (UV) Spectroscopy (Koike & Ohmoto 1992; Koike et al. 1994).



C-18 **(1)** carbon skeleton

C-19 **(2)** carbon skeleton

C-20 **(3)** carbon skeleton

C-22 **(4)** carbon skeleton

C-25 **(5)** carbon skeleton (a)

C-25 **(5)** carbon skeleton (b)

FIGURE 2. Basic skeletons of quassinoids

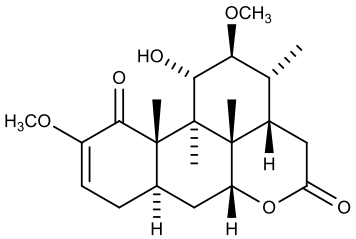
Table 1 delineates current findings on the compounds of *P. javanica.* Other than quassinoids, quassinoid glycosides, alkaloids, and triterpenoids are also extracted from the plants. Majority of the compounds found in *P. javanica* are clearly quassinoids and their glycosides (Figures 3 & 4). This has aligned with the statement indicating that quassinoids can be considered a chemotaxonomic marker of Simaroubaceae (Alves et al. 2014). Meanwhile, other constituents present in *P. javanica* are alkaloids and triterpenoids, as shown in Figures 5 and 6.

TABLE 1. Chemical constituents of *P. javanica*

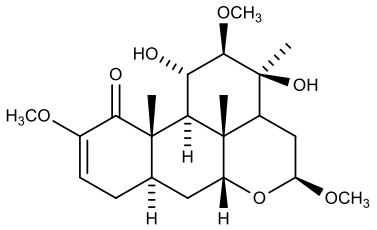
Compound class	Chemical constituents	Part of plants	Reference
Quassinoids	Javanicins A (6), C (7), D (8)	Stembarks	(Ohmoto et al. 1989)
Quassinoids	Javanicin B **(9)**	Barks	(Koike & Ohmoto 1990)
	Javanicins E **(10)**, F **(11)**, G **(12)**, M **(13)**	Barks	(Koike et al. 1990)
	Javanicins H **(14)**, I **(15)**, J **(16)**	Leaves	(Koike et al. 1991a)
	Javanicins K **(17)**, L **(18)**, O **(19)**, R **(20)**, S **(21)**	Leaves	(Koike et al. 1991b)
	Javanicin T **(22)**	Stems	(Koike et al. 1991b)
	Javanicin N **(23)**	Woods	(Koike et al. 1991b)
	Javanicins P **(24)**, Q **(25)**	Leaves	(Koike et al. 1991b)
	Javanicins U **(26)**, V **(27)**, W **(28)**	Stems	(Koike et al. 1991c)
	Javanicins X **(29)**, Y **(30)**	Barks	(Koike et al. 1991c)
	Javanicin Z **(31)**	Barks	(Koike et al. 1995)
	Dihydrojavanicin Z **(32)**	Barks	(Koike et al. 1995)
	Picrajavanins A **(33)**, B **(34)**	Barks	(Yoshikawa et al. 1993)
		Barks	(Win et al. 2015)
	Picrajavanins C **(35)**, D **(36)**, E **(37)**, F **(38)**, G **(39)**	Barks	(Win et al. 2015)
	Picrajavanins H **(40)**, I **(41)**, J **(42)**, K **(43)**, L **(44)**, M **(45)**	Barks	(Win et al. 2016a)
	(16R)-Methoxyjavanin B **(46), (16S)-**methoxyjavanin B **(47)**	Woods	(Prema et al. 2019)
	Picrasin A **(48)**	Stems	(Ishii et al. 1991)
		Barks	(Win et al. 2016a)
	Nigakilactones B **(49)**, F **(50)**	Leaves, stems	(Koike et al. 1991b)
Quassinoid Glycosides	Javanicinosides A (**51**)	Barks	(Ohmoto et al. 1989)

	Javanicinosides B **(52)**, C **(53)**	Barks	(Koike & Ohmoto 1990)
	Javanicinosides D **(54)**, F **(55)**, H **(56)**	Barks	(Ishii et al. 1991)
	Javanicinoside E **(57)**, G **(58)**	Stems	(Ishii et al. 1991)
	Javanicinosides I **(59)**, J **(60)**, K **(61)**, L **(62)**	Stems	(Koike & Ohmoto 1992)
Alkaloids	5-hydroxydehydrocrenatine **(63)**	Barks	(Arbain & Sargent 1987)
	5-hydroxycrenatine **(64)**	Barks	(Arbain & Sargent 1987)
	4-methoxy-1-vinyl-β-carboline **(65)**	Barks	(Johns et al. 1970)
	6-hydroxy-4-methoxy-1-vinyl-β-carboline **(66)**	Barks	(Pavanand et al. 1988)
	Javacarboline **(67)**	Stems	(Koike et al. 1994)
Triterpenoids	Hispidol A **(68)**	Stems	(Ishii et al. 1991)
	Lanosta-7,24-dien-3-one **(69)**	Stems	(Ishii et al. 1991)

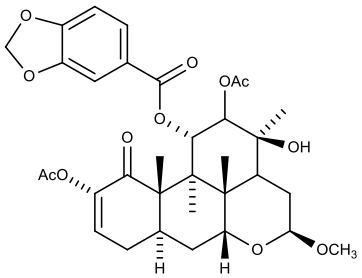
PHARMACOLOGICAL PROPERTIES



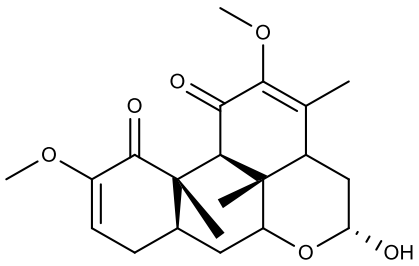
Javanicin A **(6)**



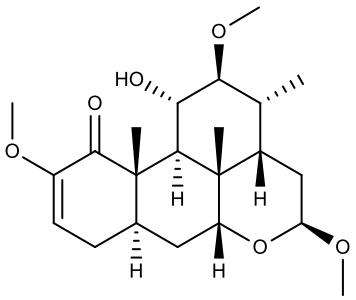
Javanicin C **(7)**



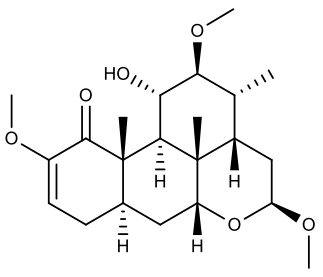
Javanicin D **(8)**



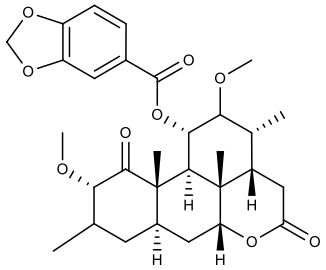
Javanicin B **(9)**



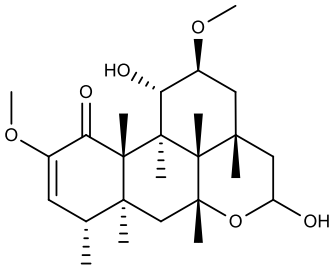
Javanicin E **(10)**



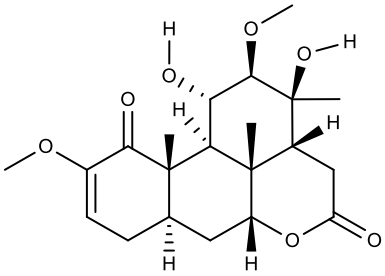
Javanicin F **(11)**



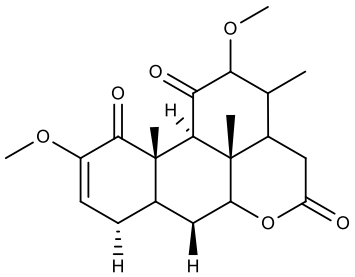
Javanicin I **(12)**



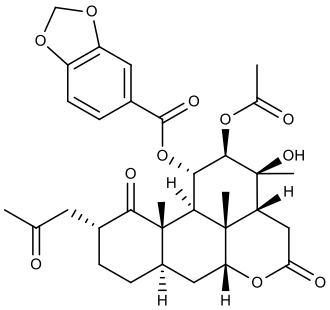
Javanicin M **(13)**



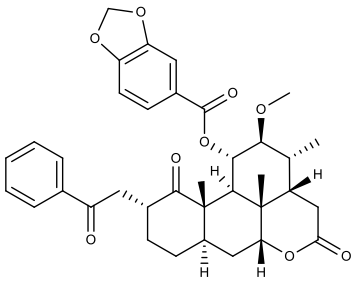
Javanicin H **(14)**



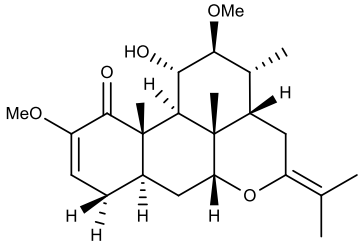
Javanicin I **(15)**



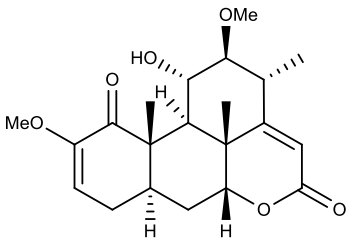
Javanicin J **(16)**



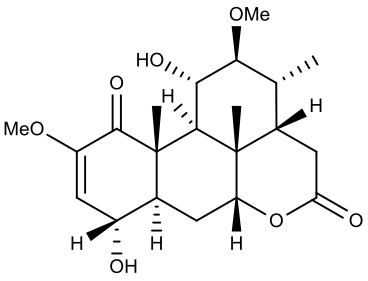
Javanicin K **(17)**



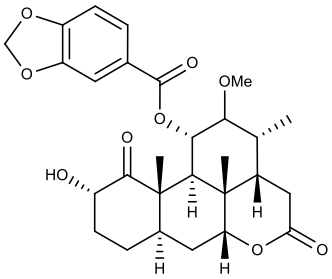
Javanicin L **(18)**



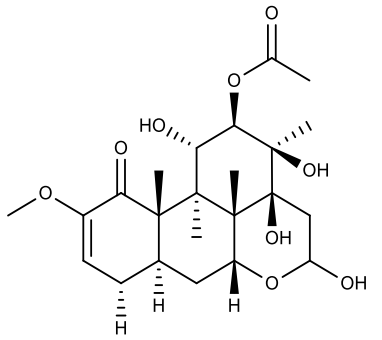
Javanicin O **(19)**



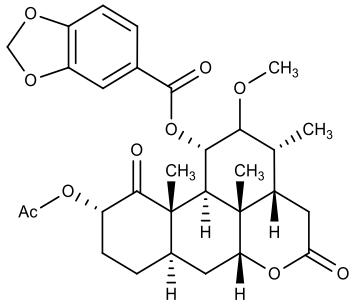
Javanicin R **(20)**



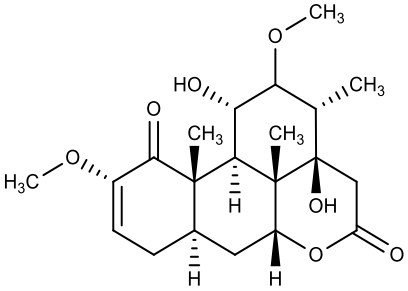
Javanicin S **(21)**



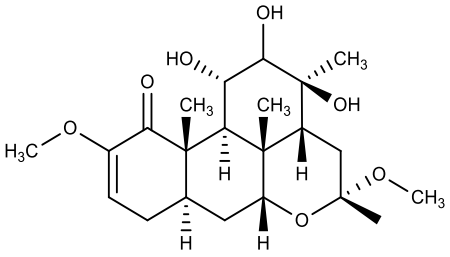
Javaicin T **(22)**



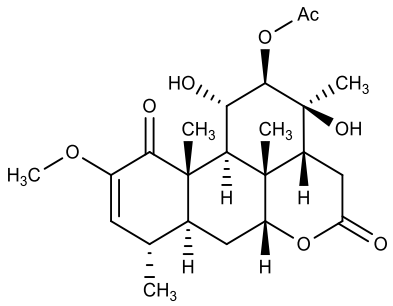
Javanicin N **(23)**



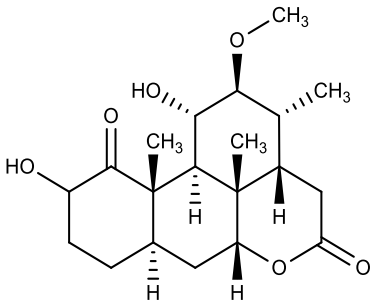
Javanicin P **(24)**



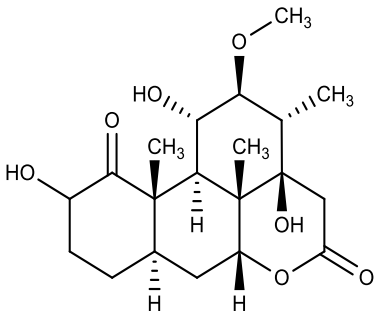
Javanicin Q **(25)**



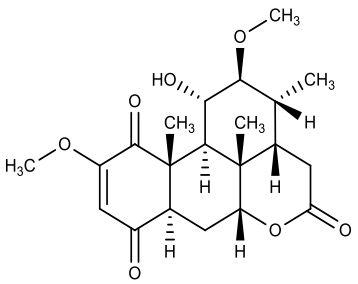
Javanicin U **(26)**



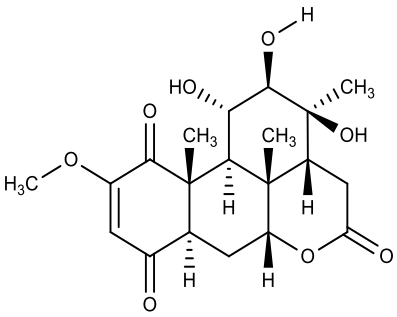
Javanicin V **(27)**



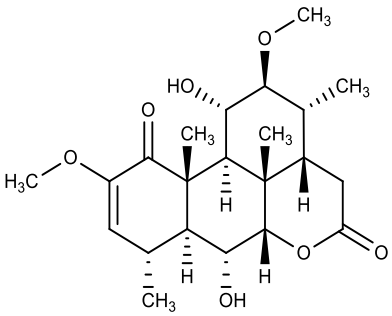
Javanicin W **(28)**



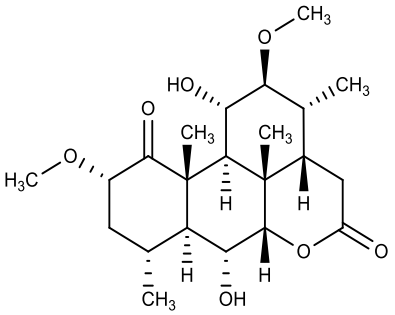
Javanicin X **(29)**



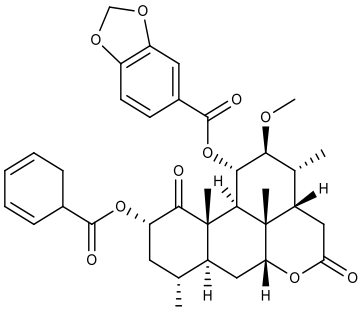
Javanicin Y **(30)**



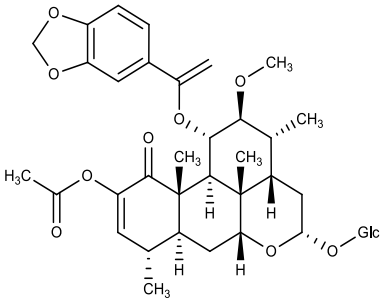
Javanicin Z **(31)**



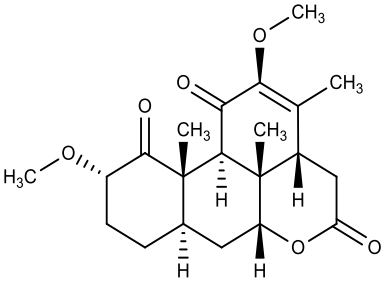
Dihydrojavanicin Z **(32)**



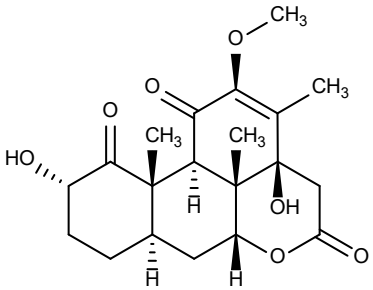
Picrajavanicin A **(33)**



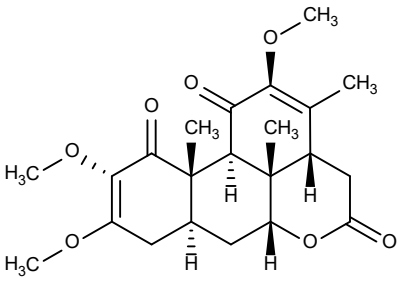
Picrajavanicin B **(34)**



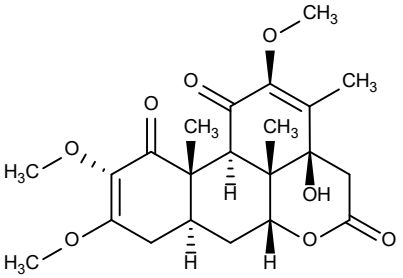
Picrajavanicin C **(35)**



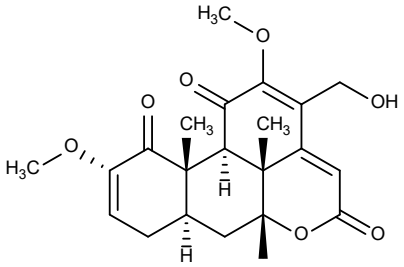
Picrajavanicin D **(36)**



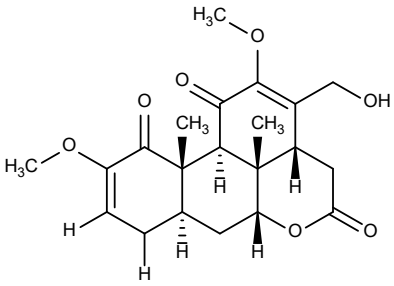
Picrajavanicin E **(37)**



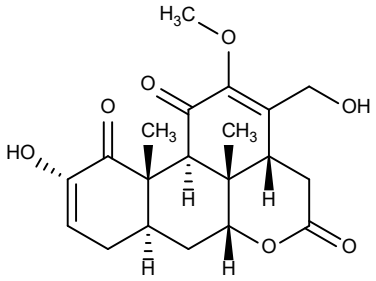
Picrajavanicin F **(38)**



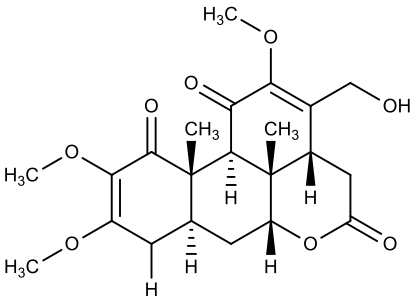
Picrajavanin G **(39)**



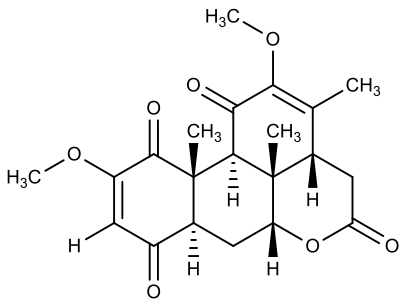
Picrajavanin H **(40)**



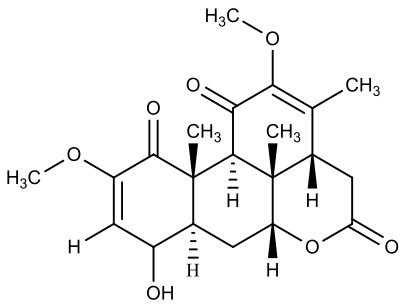
Picrajavanin I **(41)**



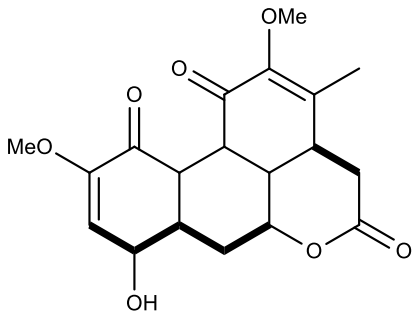
Picrajavanin J **(42)**



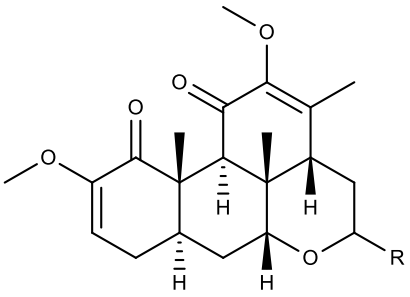
Picrajavanin K **(43)**



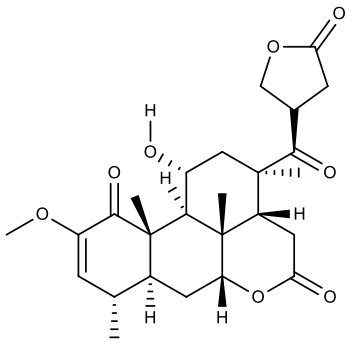
Picrajavanin L **(44)**



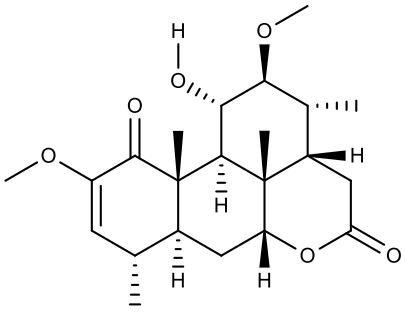
Picrajavanin M **(45)**



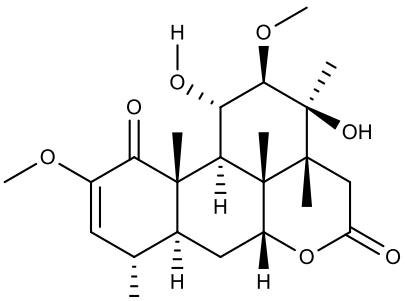
R= α-OCH_3 (16R) Methoxyjavanin B **(46)**
R= β-OCH_3 (16R) Methoxyjavanin B **(47)**



Picrasin A **(48)**

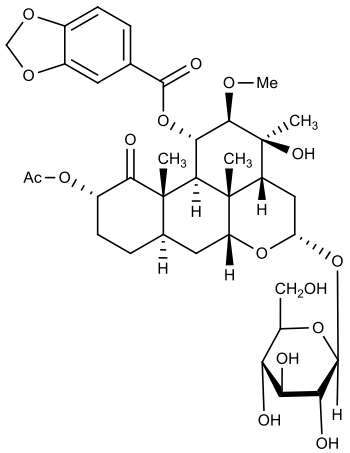


Nigakilactone B **(49)**

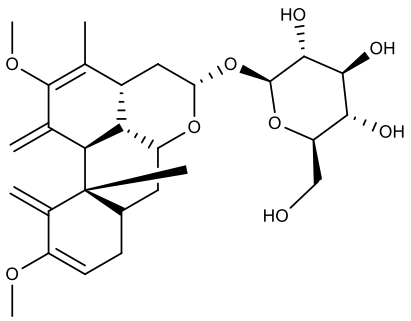


Nigakilactone F **(50)**

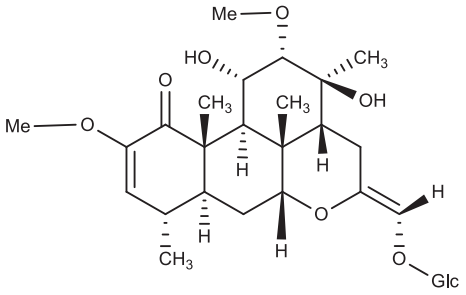
FIGURE 3. Quassinoid constituents of *P. javanica*



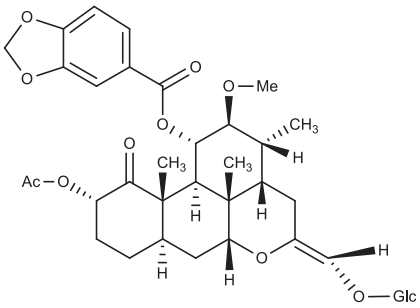
Javanicinoside B **(51)**



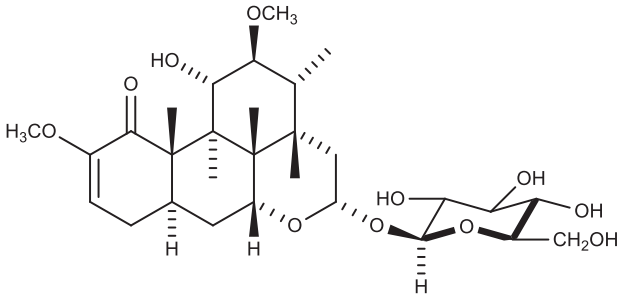
Javanicinoside C **(52)**



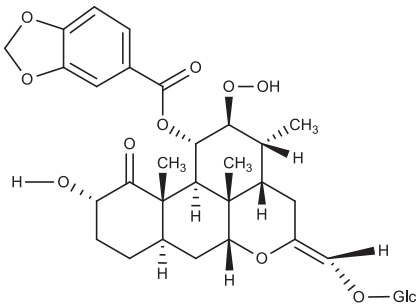
Javanicinoside D **(53)**



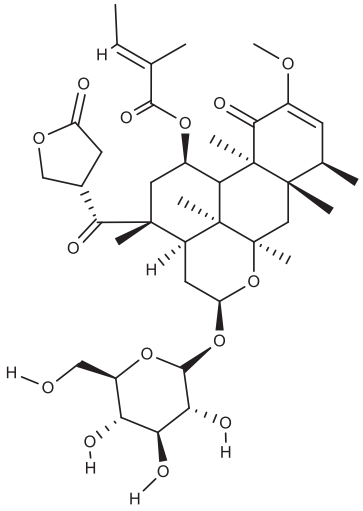
Javanicinoside F **(54)**



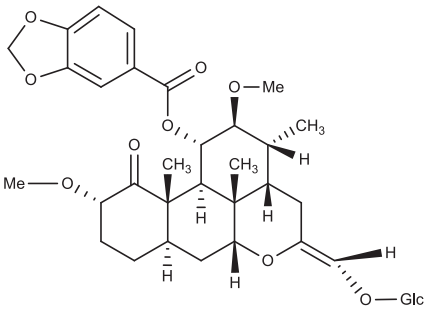
Javanicoside A **(55)**



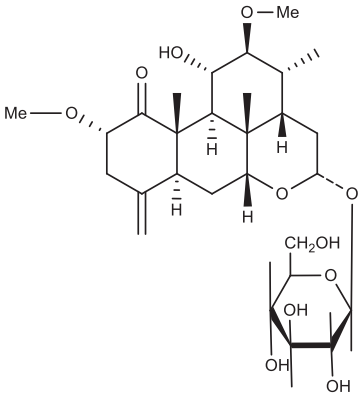
Javanicinoside H **(56)**



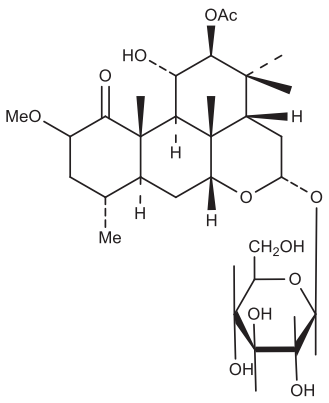
Javanicinoside E **(57)**



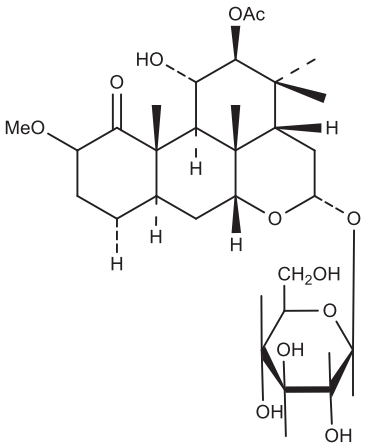
Javanicinoside G **(58)**



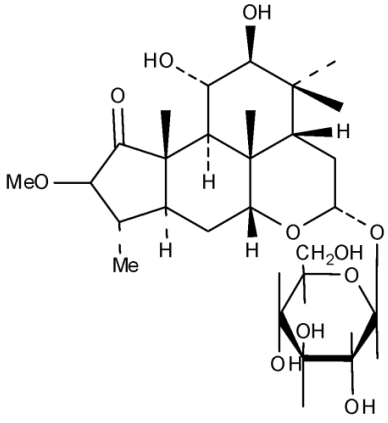
Javanicinoside I **(59)**



Javanicinoside J **(60)**

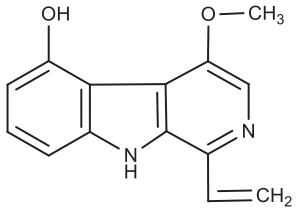


Javanicinoside K **(61)**

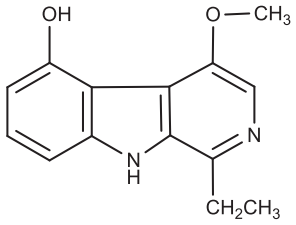


Javanicinoside L **(62)**

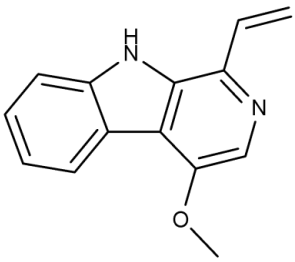
FIGURE 4. Quassinoid glycosides of *P. javanica*



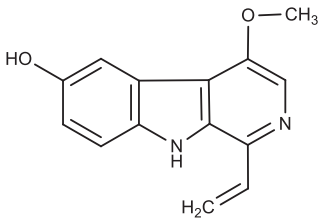
5-hydroxydehydrocrenatine **(63)**



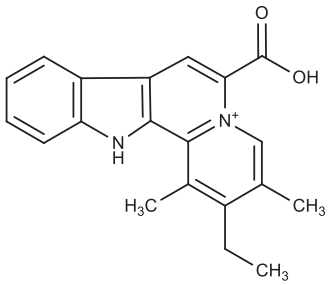
5-hydroxycrenatine **(64)**



4-methoxy-1-vinyil-β-carboline **(65)**

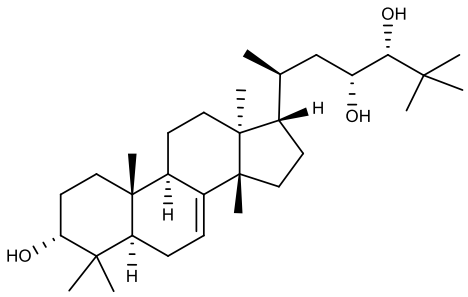


6-hydroxy-4methoxy-1vinyil-β-carboline **(66)**

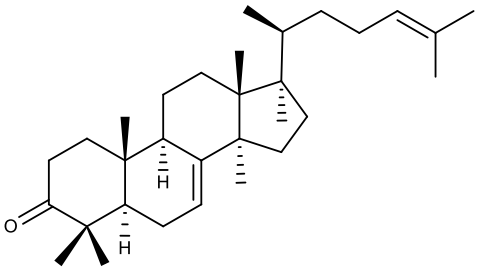


Javacarboline **(67)**

FIGURE 5. Alkaloids of *P. javanica*



Hispidol A **(68)**



Lanosta-7,24-dien-3-one **(69)**

FIGURE 6. Triterpenoids of *P. javanica*

Anti-malarial activity

The latest report by WHO (2018) has highlighted that 219 million cases of malaria was recorded in 2017, which indicated an increment from 217 million cases logged in 2016. These numbers have proven that malaria is highly prevalent around the world. According to WHO (2018), malaria is a life threatening disease caused by the *Anopheles* mosquito infection; it is one of the deadliest parasitic infections, but it is curable and preventable. Despite having effective treatments and prophylactic methods, a growing resistance by malarial parasites towards antimalarial agents has been noted. The resistance towards these antimalarial medication has driven many researchers to continuously find potential natural compounds that can be developed as an antimalarial.

Traditionally, *P. javanica* is one of the plants commonly used as an antimalarial in countries like Myanmar, Thailand, Indonesia (Saiin & Sirithunyalug 2017) and northest India (Bora et al. 2007). A decoction of its bark is generally used to treat malaria (Bora et al. 2007). Meanwhile, the plant species as a whole was previously used as antimalarial agent during World War II (Saiin & Sirithunyalug 2017). Despite the abundant information on utilizing *P. javanica* to fight against malarial parasites, studies explaining the exact compound responsible for its antimalarial property are still lacking. Earlier studies on *P. javanica* activity against malarial parasites include an *in vitro* test by Pavanand et al. (1988), which investigated its inhibitory effect against *Plasmodium falciparum* isolates. The results of the study showed that the isolated alkaloids, specifically 4-methoxy-1-vinyl-β-carboline and 6-hydroxy-4-methoxy-1-vinyl-β-carboline, possessed some antimalarial activity, though it was lesser compared to mefloquine, another antimalarial agent. Furthermore, these researchers underlined the possibility of *in vivo* metabolism in converting these compounds to active metabolites, which was not detected in the *in vitro* test. A similar study done by Saiin et al. (2003) looked into different crude extracts from *P. javanica* stem bark, which showed the hexane extract as having the highest *in vitro* antimalarial activity against *P. falciparum*. Afterwards, further fractionations were undertaken to identify which compound had provided more activity against malarial parasites. The results showed that β-sitosterol was a major compound in the fraction having the highest inhibitory activity, but its poor solubility in dimethyl sulfoxide did not permit further antimalarial investigation. Meanwhile, other isolated compound, β-sitosterol showed inhibitory effects against *P. falciparum*. However, these fractions would require further fractionation to establish the exact compound that is exhibiting antimalarial activity.

Among indole alkaloids extracted from *P. javanica* showing 14 purified indole compounds, however, only two compounds (4-methoxy-1-vinyl-β-carboline and 6-hydroxy-4-methoxy-1-vinyl-β-carboline) were assessed regarding their antimalarial activity, while the review demonstrated the scarcity of studies on indole alkaloids extracted from *P. javanica* (Saiin & Sirithunyalug 2017). In addition, Takasu et al. (2005) synthesized several β-carbolines and their corresponding salts, which had a pi-delocalized lipophilic cationic structure, for evaluating both *in vivo* and *in vitro* activities of these compounds against malaria. These compounds and their quaternary carbolinium cations were found to have positive antimalarial action, whereby the cations were found to provide more selective toxicity against malarial parasites. The finding offered a perspective for new research

regarding the potential behind *P. javanica* as novel source for antimalarial agent.

Previously, only indole alkaloids of *P. javanica* have been mentioned to pose antimalarial activity. However, quassinoids as another group of compounds that can be found in *P. javanica* also offers activity against malarial parasites. For instance, Paptiwi et al. (2007) corroborated that the extracts from *P. javanica* stem bark and leaves are equipped with the ability to reduce parasitemia induced in mice better compared to chloroquine. The assumption was that such effect was due to the presence of alkaloids and quassinoids in the plant, which could also be found in other members of Simaroubaceae. Therefore, they should exhibit similar inhibitory activity against malarial parasites. This has resulted in the studies on the antimalarial activity of quassinoids from the plant family, whereby several have suggested its function as an antimalarial is via protein synthesis disruption and followed by nucleic acid inhibition. Such mechanism is fundamentally different than that of chloroquine (Kirby et al. 1989) demonstrating the possibility of plants from the family to be a source of antimalarial drugs. Furthermore, the ester moiety of quassinoids have been found to contribute towards higher antimalarial activity compared to those without it (Ekong et al. 1990; O'Neill et al. 1986). These types of studies have served a head start in explicating the manner in which compounds from *P. javanica* work against malarial parasites.

Through these findings, it can be inferred that there are minimal studies done on the antimalarial activity of *P. javanica,* despite its proven activity against malaria and its extensive usage traditionally in some countries as a treatment. These reasonings should thus further advocate the initiation for more research on the antimalarial properties of the plant.

Antiproliferative activity

Cancer is a disease in which abnormal cell growth occurs and spread to other parts of the body. WHO (2018) has proclaimed that it can kill one in six people annually, despite recent statement that cancer management is possible in case of early diagnosis, immediate treatment, and palliative care for cancer patients. Therefore, effective cancer treatment plays a major role in preventing mortality due to cancer, thus, encouraging researchers to find novel antitumor compounds sourced from natural products so as to vary the therapeutic agent choices available. These new compounds may be studied extensively and designed to have more specificity towards cancer cells, as most of the available anticancer agents are known to target the cancer cells and normal healthy cells alike.

Studies have shown that *P. javanica* possesses some degree of antiproliferative and cytotoxic activity, which are among the pertinent characteristics of an anticancer agent. However, they have employed different methods to assess the plant's anticancer property. During the initial research on *P. javanica* activity against cancer, Koike et al. (1994) first discovered its cytotoxicity activity while isolating a β-carboline alkaloid, namely javacarboline, from its stem. Such property was thus attributed to this particular compound since it exhibited *in vitro* cytotoxicity against human tumor PC-6 cells and murin lymphocytic leukemia P-388 cells at GI_{50} values of 35.9 μg/mL and 32.5 μg/mL, respectively. Meanwhile, a more recent study by Sharmin et al. (2012) has utilized the brine shrimp lethality bioassay to assess the anticancer activity of *P. javanica*. This particular bioassay was used to indicate the plant's cytotoxicity, as well as the other pharmacological properties of anticancer, antiviral, and pesticidal effects. Through this method, it was found that the crude extracts contained potent bioactive compounds, with the lowest LC_{50} value obtained of 1.04 ± 0.31 μg/mL. This allowed the suggestion for further fractionation of the crude extracts so as to identify the exact compound that was exerting the cytotoxicity effect.

Moreover, Win et al. (2015) showed that the chloroform extract of *P. javanica* posed antiproliferative activity against five human cancer cell lines (i.e. A549, HeLa, PANC-1, PSN-1, and MDA-MB-231). The *in vitro* antiproliferative evaluation was executed with 5-fluorouracil as a positive control to compare with the activity shown by the extract against five selected cancer cell lines. The extract consequently showed its antiproliferative activity with IC_{50} values between 1.6 and 22.1 μg/mL. The same extract was then separated via chromatographic method and resulted in the characterization of 10 quassinoids (i.e. picrajavanicins A, B, C, D, E, F, and G, and javanicins B, F and I). However, each of the isolates did not show any antiproliferative activity, which led to the postulation that the antiproliferative property found in the chloroform extract may be accredited to the other quassinoids and β-carboline alkaloids in *P. javanica*. These studies have ultimately shown that the plant does have anticancer activity, though more in-depth investigations are needed to recognize which compound has contributed to such activity.

Another study conducted on *P. javanica* resulted in the isolation of eight tetracyclic quassinoids from the chloroform extract of its bark (i.e. picrajavanicins H, I, J, K, L, and M; and picrasin A and 2'-isopicrasin

A). An evaluated of its antiproliferative activity has shown that these quassinoids is active against human pancreatic cancer PANC- 1 cell line. Moreover, picrasin A and 2' isopicrasin A were found to have additional antiproliferative activity in human cervical cancer HeLa cell lines. In contrast to the aforementioned studies, the study conducted an additional analysis on the structure-activity relationships (SARs) of the discovered quassinoids. Such pursuit led the researchers to certify the significance of the substituents at C-4 and C-13 towards the activity against pancreatic cancer PANC-1 cell lines (Win et al. 2016a). Such findings have provided supplementary information on the anticancer activity of *P. javanica,* which may be helpful in the future development of anticancer agents sourced from this plant species.

Nevertheless, another study has shown that the bark extracts of *P. javanica* has no anticancer activity (Zuhrotun et al. 2015), which is contradictor against previous findings. The study utilized the mechanism-based yeast bioassay to check the antiproliferative effect of several Indonesian plants of the Apocynaceae, Simaroubaceae, and Magnoliaceae families. The bioassay was a panel of yeast strains used to see whether any inhibition zone was produced when yeast growth was prohibited. Such activity was assessed by calculating the required concentration of sample for producing an inhibition zone of 12 mm around a well. Generally, compounds that give positive results are topoisomerase inhibitors, a commonly utilized DNA damaging agent incorporated in anticancer treatment. Based on these results, Zuhrotun et al. (2015) affirmed *P. javanica*'s inactive role as an anticancer agent. Regardless, the current study may justify the mechanism behind *P. javanica* as an anticancer agent, thus, becoming a gateway to establish such property.

Antiviral activity

An infection of the human immunodeficiency virus type 1 (HIV-1) induces the host cells to activate innate and cellular immune responses for the purpose of limiting the viral invasion. In contrast, HIV opts for many strategies to counteract such host cell responses, one of which being the virion-associated accessory protein called viral protein 1 (Vpr). It consists of 96 amino acids and has the molecular weight of a basic protein (i.e. 14 kDa). This protein is involved in the pathogenesis and viral replication of HIV, thus resulting in the promotion of the viral infection (Li et al. 2009). For this reason, inhibiting Vpr may be helpful for the infected patient via halting viral replication processes, thus opening up for more opportunities in the development of anti-HIV therapy. Besides, Vpr is said to be a good drug target in the acquired immunodeficiency syndrome (AIDS) therapy (Stewart et al. 2000). Consequently, such opportunity may be used to foster the findings of natural compounds as new anti-HIV agents.

The potential of *P. javanica* as a source of antiviral protein R has been discovered in a study that evaluated quassinoids isolated from the plant with regard to their inhibitory effect on Vpr expression (Win et al. 2016b). The study demonstrated the newly discovered property to vastly differ compared to other plant species exhibiting similar inhibitory effects, in terms of its SARs. Overall, quassinoids with a methyl group at C-13 and hydroxy group at C-16 are the compounds exhibiting the most Vpr inhibitory activity. Similarly, the presence of hydroxy at C-14 and carbonyl at C-4 and the absence of methoxy at C-3 collectively increase the inhibition, albeit being less significant considerations compared to the substitutions in C-13 and C-16. Such comprehensive study has provided information utilizable by researchers in synthesizing antiviral agents.

It should be noted that the previously mentioned study is the only report of *P. javanica* activity against virus, underlining the rarity of investigations on this plant. In contrast, other plant species in the Simaroubaceae family have been explored in several investigations to discover their antiviral properties (Nawawi et al. 1999; Rashed et al. 2013). These studies may be helpful to some degree, especially since plants of the family have similar compound characteristics. For instance, Nawawi et al. (1999) affirmed that *Eurycoma longifolia* posed an inhibitory activity against herpes simplex virus type 1 (HSV-1), exhibiting strong toxicity *in vivo* and *in vitro* alike. Therefore, extra precautionary steps are needed if the plant is to be developed as antivirals. Meanwhile, another study has isolated a quassinoid compound named simalikalactone D from the chloroform crude extract of *Quassia africana*. This compound has been found to be responsible for the pronounced antiviral activity of the plant against several viruses (Apers et al. 2002). Furthermore, the researchers have postulated that the ester group at C-15 and epoxymethano bridge between C-8 and C-13 may be the compound features contributing to such activity. Additionally, *Ailanthus excelsa* as another plant of the Simaroubaceae family has shown similar antiviral activity when in the form of chloroform extract as opposed methanol extract (Rashed et al. 2013).

In short, although not many studies have been done on the antiviral activity of *P. javanica* and other plants of the Simaroubaceae family, the available studies are sufficiently significant and provide some knowledge

regarding the possibility of developing antiviral agents from these natural sources.

Antimicrobial activity

The search for new antimicrobial agents so as to overcome antibiotic resistance in microorganisms is very challenging. Khan et al. (2001) reported that all extracts and fractions of *P. javanica* exhibited a broad spectrum of antibacterial activity, but none worked against the tested molds. The bacteria and protozoa used in the experiment included the Bacillus species, Micrococcus species, Staphylococcus species, *Pseudomonas aeruginosa,* and *Salmonella typhi*. The only report on *P. javanica'*s antibacterial activity may thus be very helpful in future research with regard to this particular attribute.

Similarly, other members of the Simaroubaceae family have been reported to possess antibacterial activity, whereby *Ailanthus altissima* extracts display antibacterial activity against different bacteria and fungi (Poljuha et al. 2017; Rahman et al. 2009). Other plants of the family showing antibacterial activity in different extracts include *Simaba ferruginea* (Gazoni et al. 2018) and *Samadera indica* (Viswanad et al. 2012).

Membrane stabilizing activity

The membrane-stabilizing action of natural products has been investigated previously to assess their anti-inflammatory activities (Omale & Okafor 2008; Yoganandam et al. 2010). Various disorders arise from the release of lysosomal enzymes during inflammation, whereby common anti-inflammatory agents used (i.e. non-steroidal drugs (NSAIDs)) function by impeding them or stabilizing their membranes (Yoganandam et al. 2010). With this in mind, natural compounds are continuously assessed for their anti-inflammatory activity, regardless of their mechanism of action.

P. javanica has been found to yield membrane-stabilizing activity via the utilizations of hypotonic solution and heat-induced hemolysis of human red blood cells (RBCs). The plant's extracts have prevented human RBCs membrane from lysing due to such hypotonic solution and heat (Sharmin et al. 2013). Despite it being the only study that describes the membrane-stabilizing activity of *P. javanica*, the study has equipped scholars for further investigation regarding the compounds in the plant with regard to this activity.

Other plants of the family have also exhibited similar activity, which include *E. longifolia*, *A. excels,* and *S. indica* (Rajalakshmi & Harindran 2013). These studies have employed the same method as that by Sharmin et

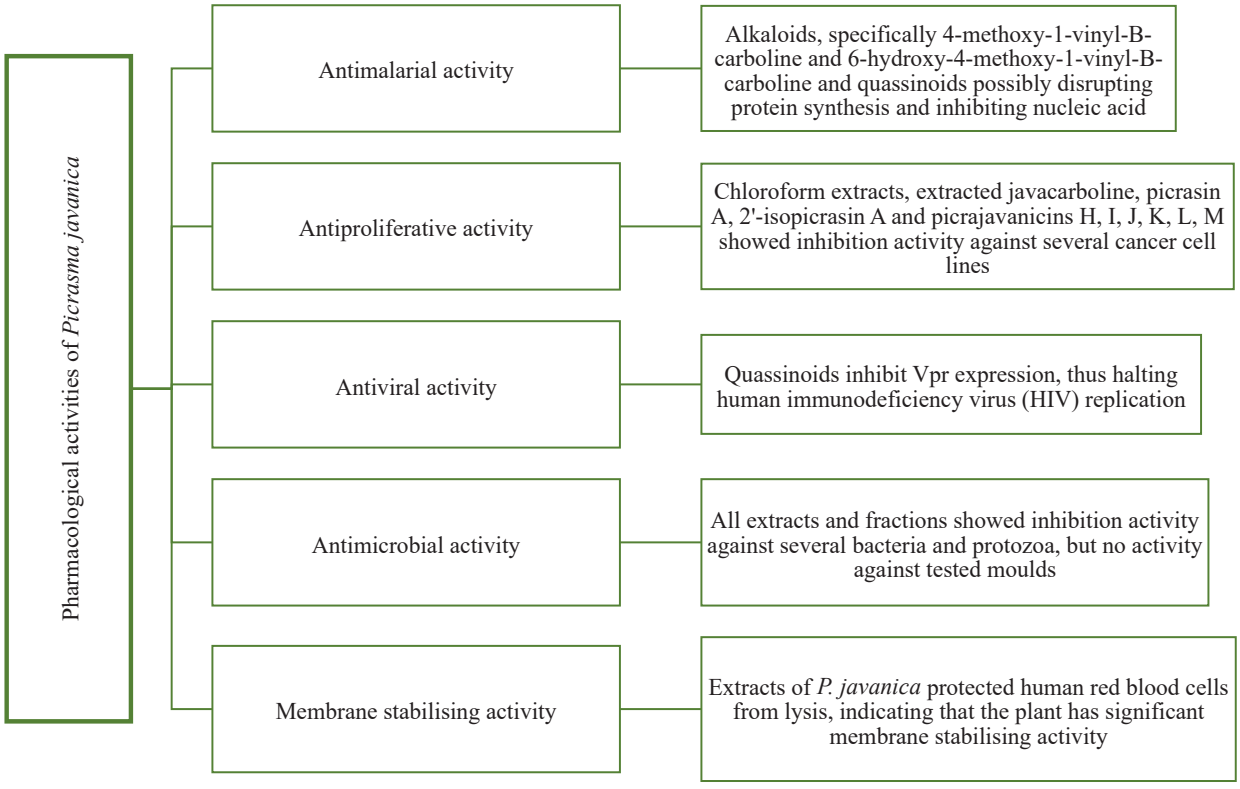


FIGURE 7. Summary of pharmacological activities exhibited by *P. javanica*

al. (2013) to assess the membrane-stabilizing activity of the respective plants. However, these researches must be further evaluated to identify and isolate the active chemical constituents responsible for the activity, thus leading towards the discovery of new and natural anti-inflammatory agents. A summary of the pharmacological activities shown by *P. javanica* is grouped in Figure 7.

Conclusions

Picrasma javanica, also known as *P. nepalensis* or *P. philippinensis,* is a plant of the Simaroubaceae plant family, commonly recognized for bitter group of compounds present in them, namely quassinoids. Some of the compounds isolated from the varying parts of the plant as of today include quassinoids, alkaloids, and triterpenoids, which have exhibited interesting pharmacological activities. The properties that have been studied so far are their antimalarial, antiproliferative, antiviral, antimicrobial, and membrane-stabilizing activities. Evidently, most of the available studies have discovered that the activities displayed by the extracts of *P. javanica* are due to the key players of quassinoids and alkaloids. Although the mechanism of action and further details regarding the plant such as specific compounds that induce these activities are unclear and lacking, it is clear that *P. javanica* does have therapeutic benefits for mankind. Therefore, further investigation should be conducted to discover its potential therapeutic effects in the context of clinical significance.

Acknowledgements

The authors are thankful to the International Islamic University Malaysia for funding this work via Grant No. FRGS/1/2019/WAB01/UIAM/02/5. The authors would like to declare that there is no conflict of interest.

References

Alves, I.A.B.S., Miranda, H.M., Soares, L.A.L. & Randau, K.P. 2014. Simaroubaceae family: Botany, chemical composition and biological activities. *Brazilian Journal of Pharmacognosy* 24: 481-501.

Apers, S., Cimanga, K., Vanden Berghe, D., Van Meenen, E., Otshudi Longanga, A., Foriers, A., Vlietinck, A. & Pieters, L. 2002. Antiviral activity of simalikalactone D, a quassinoid from *Quassia africana*. *Planta Med.* 68: 20-24.

Arbain, D. & Sargent, M.V. 1987. The alkaloids of *Picrasma Javanica. Australian Journal of Chemistry* 40: 1527-1536.

Bora, U., Sahu, A., Saikia, A.P., Ryakala, V.K. & Goswami, P. 2007. Medicinal plants used by the people of Northeast India for curing malaria. *Phytotherapy Research* 21: 800-804.

Curcino Vieira, I.J. & Braz-Felho, R. 2006. Quassinoids: Structural diversity, biological activity and synthetic studies. *Studies in Natural Product Chemistry* 33: 433-492.

Ekong, R.M., Kirby, G.C., Patel, G., David Phillipson, J. & Warhurst, D.C. 1990. Comparison of the *in vitro* activities of quassinoids with activity against *Plasmodium falciparum*, anisomycin and some other inhibitors of eukaryotic protein synthesis. *Biochem. Pharmacol.* 40: 297-301.

Gazoni, V.F., Balogun, S.O., Arunacham, K., Oliveira, D.M., Filho, V.C., Lima, S.R., Colodel, E.M., Soares, I.M., Ascêncio, S.D. & de Oliveira Martins, D.T. 2018. Assessment of toxicity and differential antimicrobial activity of methanol extract of rhizome of *Simaba ferruginea* A. St.-Hil. and its isolate canthin-6-one. *J. Ethnopharmacol.* 223: 122-134.

Globinmed - *Picrasma javanica* Blume. http://www.globinmed.com/index.php?option=com_content&view=article&id=105500:picrasma-javanica-blume-r&catid=286&Itemid=357. Assessed on 14 November 2019.

Ishii, K., Kazuo, K. & Ohmoto, T. 1991. Javanicinosides D-H, quassinoid glucosides from *Picrasma javanica*. *Phytochemistry* 30(12): 4099-4103.

Johns, S.R., Lamberton, J.A. & Sioumis, A.A. 1970. 4-Methoxy-1-vinyl-β-carboline, a new alkaloid from *Picrasma javanica* (simaroubaceae). *Australian Journal of Chemistry* 23(3): 629-630.

Khan, M.R., Kihara, M. & Omoloso, A.D. 2001. Antibacterial activity of *Picrasma javanica*. *Fitoterapia* 72: 406-408.

Kirby, G.C., O'Neill, M.J., Phillipson, J.D. & Warhurst, D.C. 1989. *In vitro* studies on the mode of action of quassinoids with activity against chloroquine-resistant *Plasmodium falciparum*. *Biochemical Pharmacology* 38: 4367-4374.

Koike, K. & Ohmoto, T. 1992. New quassinoid glucosides, javanicinosides I, J, K, and L, from *Picrasma javanica*. *Journal Natural Products* 55: 482-486.

Koike, K. & Ohmoto, T. 1990. Quassinoids from *Picrasma javanica*. *Phytochemistry* 29(8): 2617-2621.

Koike, K., Yokoh, M., Furukawa, M., Ishii, S. & Ohmoto, T. 1995. Picrasane quassinoids from *Picrasma javanica*. *Phytochemistry* 40(1): 233-238.

Koike, K., Ohmoto, T., Uchida, A. & Oonishi, I. 1994. Javacarboline, a new β-carboline alkaloid from the stem of *Picrasma javanica* in Java. *Heterocycles* 38: 1413-1420.

Koike, K., Ishii, K., Mitsunaga, K. & Ohmoto, T. 1991a. Quassinoids from *Picrasma javanica*. *Phytochemistry* 30(3): 933-936.

Koike, K., Ishii, K., Mitsunaga, K. & Ohmoto, T. 1991b. New des-4-Methylpicrasane quassinoids from *Picrasma javanica*. *Journal of Natural Products* 54(3): 837-843.

Koike, K., Ishii, K., Mitsunaga, K. & Ohmoto, T. 1991c. New quassinoids from *Picrasma javanica*: Structures of Javanicins U, V, W, X and Y. *Chemical and Pharmaceutical Bulletin* 39(8): 2021-2023.

Koike, K., Mitsunaga & Ohmoto, T. 1990. New quassinoids from Indonesia *Picrasma javanica*. Structures of Javanicins E,F,G and M. *Chemical & Pharmaceutical Bulletin* 38(10): 2746-2749.

Li, G., Bukrinsky, M. & Zhao, R. 2009. HIV-1 viral protein R

(VPR) and its interactions with host cell. *Curr. HIV Res.* 7: 178-183.

Nawawi, A., Nakamura, N., Hattori, M., Kurokawa, M. & Shiraki, K. 1999. Inhibitory effects of Indonesian medicinal plants on the infection of herpes simplex virus type 1. *Phytother. Res.* 13: 37-41.

O'Neill, M.J., Bray, D.H., Boardman, P., Phillipson, J.D., Warhurst, D.C., Peters, W. & Suffness, M. 1986. Plants and sources of antimalarial drugs: *In vitro* antimalarial activities of some quassinoids. *Antimicrob. Agents Chemotherapy* 30: 101-104.

Ohmoto, T., Koike, K., Mitsunaga, K., Fukuda, H. & Kagei, K. 1989. Studies on the constituents of Indonesian *Picrasma javanica*. III. Structures of new quassinoids, javanicins A, C and D. *Chem. Pharm. Bull.* 37: 2991-2994.

Omale, J. & Okafor, P.N. 2008. Comparative antioxidant capacity, membrane stabilization, polyphenol composition and cytotoxicity of the leaf and stem of *Cissus multistriata*. *African Journal of Biotechnology* 7: 3129-3133.

Paptiwi, Harapini, M. & Chairul. 2007. Uji aktivitas antimalaria secara *in-vivo* ekstrak Ki Pahit (*Picrasma javanica*) pada mencit yang diinfeksi *Plasmodium berghei*. *Biodiversitas* 8: 111-113.

Pavanand, K., Yongvanitchit, K., Webster, H.K., Dechatiwongse, T., Nutakul, W., Jewvachdamrongkul, Y. & Bansiddhi, J. 1988. *In vitro* antimalarial activity of a Thai medicinal plant *Picrasma javanica* Bl. *Phytotherapy Research* 2: 33-36.

Poljuha, D., Sladonja, B., Šola, I., Dudaš, S., Bilić, J., Rusak, G., Motlhatlego, K.E. & Eloff, J.N. 2017. Phenolic composition of leaf extracts of *Ailanthus altissima* (Simaroubaceae) with antibacterial and antifungal activity equivalent to standard antibiotics. *Natural Product Communications* 12: 1609-1612.

Polonsky, J. 1973. Quassinoid bitter principles. In *Fortschritte Der Chemie Organischer Naturstoffe* 47: 101-150.

Prema, Wong, C.P., Nugroho, A.E., Awouafack, M.D., Win, Y.Y., Win, N.N., Ngwe, H., Morita, H. & Morita, H. 2019. Two new quassinoids and other constituents from *Picrasma Javanica* wood, and their biological activities. *Journal of Natural Medicines* 73(3): 589-596.

Rahman, A., Kim, E.L. & Kang, S.C. 2009. Antibacterial and antioxidant properties of *Ailanthus altissima* swingle leave extract to reduce foodborne pathogens and spoiling bacteria. *Journal of Food Safety* 29: 499-510.

Rajalakshmi, R.R. & Harindran, J. 2013. Anti-inflammatory activity of *Samadera indica* leaves by membrane stabilization. *IJPSR* 4: 721-723.

Rashed, K., Ataa, S. & Ahamed, M. 2013. Antiviral activity and phytochemical analysis of *Alianthus excelsa* Roxb bark. *Journal of Forest Products & Industries* 2: 30-33.

Saiin, C. & Sirithunyalug, B. 2017. Review of the chemical structures and antimalarial activities of indole alkaloids isolated from *Picrasma javanica* Bl. *Adv. Med. Plant Res.* 5: 29-36.

Saiin, C., Rattanajak, R., Kamchonwongpaisan, S., Ingkaninan, K., Sukontason, K., Baramee, A. & Sirithunyalug, B. 2003. Isolation and *in vitro* antimalarial activity of hexane extract from Thai *Picrasma javanica* B1 stembark. *Southeast Asian J. Trop. Med. Public Health* 34(Suppl 2): 51-55.

Sharmin, T., Islam, F., Sikder, M.A.A, Kabir, S., Haque, M.R. & Rashid, M.A. 2013. Membrane Stabilizing and Preliminary Hypoglycemic Activities of *Picrasma javanica*. *Bangladesh Pharm J.* 16: 89-92.

Sharmin, T., Islam, F., Kaisar, M.A., Uddin, M.G. & Rashid, M.A. 2012. Antioxidant, thrombolytic and cytotoxic activities of *Picrasma javanica*. *Dhaka University Journal of Pharmaceutical Sciences* 11: 71-74.

Stewart, S.A., Poon, B., Song, J.Y. & Chen, I.S.Y. 2000. Human immunodeficiency virus type 1 Vpr induces apoptosis through caspase activation. *Journal of Virology* 74: 3105-3111.

Takasu, K., Shimogama, T., Saiin, C., Kim, H.S., Wataya, Y., Brun, R. & Ihara, M. 2005. Synthesis and evaluation of β-carbolinium cations as new antimalarial agents based on π-delocalized lipophilic cation (DLC) hypothesis. *Chemical & Pharmaceutical Bulletin* 53: 653-661.

Viswanad, V., Aleykutty, N.A., Jayakar, B., Zacharia, S.M. & Thomas, L. 2012. Development and evaluation of antimicrobial herbal formulations containing the methanolic extract of *Samadera indica* for skin diseases. *J. Adv. Pharm. Tech. Res.* 3(2): 106-111. DOI: 10.4103/2231-4040.97285.

WHO. 2018. https://www.who.int/news-room/fact-sheets/detail/malaria. Assessed on 15 November 2019.

Win, N.N., Ito, T., Ismail, Kodama, T., Win, Y.Y., Tanaka, M., Okamoto, Y., Imagawa, H., Ngwe, H., Asakawa, Y., Abe, K. & Morita, H. 2016a. Picrajavanicins H-M, new quassinoids from *Picrasma javanica* collected in Myanmar and their antiproliferative activities. *Tetrahedron* 72: 746-752.

Win, N.N., Ito, T., Win, Y.Y., Ngwe, H., Kodama, T., Abe, I. & Morita, H. 2016b. Quassinoids: Viral protein R inhibitors from *Picrasma javanica* bark collected in Myanmar for HIV infection. *Bioorganic & Medical Chemistry Letters* 26: 4620-4624.

Win, N.N., Ito, T., Ismail, Kodama, T., Win, Y.Y., Tanaka, M., Ngwe, H., Asakawa, Y., Abe, I. & Morita, H. 2015. Picrajavanicins A-G, Quassinoids from *Picrasma javanica* collected in Myanmar. *Journal of Natural Products* 78: 3024-3030.

Yoganandam, G.P., Ilango, K. & Sucharita, D. 2010. Evaluation of anti-inflammatory and membrane stabilizing properties of various extracts of *Punica granatum* L. (Lythraceae). *International Journal of PharmTech Research* 2: 1260-1263.

Yoshikawa, M., Harada, E., Aoki, S., Yamahara, J., Murakami, N., Shibuya, H. & Kitagawa, I. 1993. Indonesian medicinal plants. VI. On the chemical constituents of the bark of *Picrasma javanica* bl. (Simaroubaceae) from Flores Island. Absolute stereostructures of Picrajavanins A and B. *Chemical and Pharmaceutical Bulletin* 41(12): 2101-2105.

Zuhrotun, A., Suganda, A.G., Wirasutisna, K.R. & Wibowo, M.S. 2015. Anticancer screening of selected Apocynaceae, Simaroubaceae and Magnoliaceae of Indonesian plants using mechanism-based yeast bioassay. *International Journal of Pharmaceutical Sciences Review and Research* 35: 90-94.

*Corresponding author; email: deny@iium.edu.my