BIOLOGY, MEDICINE, & NATURAL PRODUCT CHEMISTRY ISSN 2089-6514 (paper)
Volume 11, Number 1, April 2022 | Pages: 65-73 | DOI: 10.14421/biomedich.2022.111.65-73 ISSN 2540-9328 (online)

Ethnomedicinal, Phytochemicals, and Pharmacological Aspects of Sentul (*Sandoricum koetjape*)

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Manuscript received: 09 March, 2022. Revision accepted: 05 April, 2022. Published: 18 April, 2022.

Abstract

Sentul (Sandoricum koetjape) is a tropical plant that has been used as traditional medicine in some Asian countries for decades. Research on phytochemicals and pharmacological activities of this plant extracts has been conducted and shows promising medicinal properties. This review aims to integrate knowledge about *S. koetjape* focusing on three main aspects namely ethnomedicinal, phytochemicals, and pharmacological, in order to encourage further research on this plant for future drug development. Traditionally, all plant parts of *S. koetjape* have been used for treating various health problems and diseases such as diarrhea, fever, colic, and leucorrhoea. More than 30 chemicals have been identified from *S. koetjape*, which the most important compounds are ring-A secotriterpene, oleane-type triterpene, secomultiflorane-type triterpene, hydroxymultiflorane triterpene, and limonoids. *In vitro* studies showed pharmacological potential of the extracts and phytochemicals constituents of *S. koetjape* including antibacterial, antifungal, antitumoral, anticancer, insecticide, and antioxidant.

Keywords: Ethnomedicine; Pharmacology; Phytochemicals; *Sandoricum koetjape*; Sentul.

INTRODUCTION

Since prehistoric times, human have been utilized medicinal plants for their health benefits, as evidently shown by fossil records from the Middle Paleolithic age, approximately 60,000 years ago (Solecki, 1975; Fabricant and Farnsworth, 2001). The oldest written evidence of the utilization of the medicinal plants for drugs preparation has been verified by the 5000 years old Sumerian clay slab which described 12 drug synthesis recipes by referring to more than 250 plants (Srivastava, 2018). In addition, traditional medicines such as Ayurveda, Traditional Chinese Medicine, Unani, Traditional Korean Medicine, and Kampo have applied medicinal plants to alleviate and treat wide range of diseases such as malaria, diarrhoea, and microbial infections (Yuan et al. 2016). Currently, it is estimated that about 80% of the world's population still depend on herbs and herbal products for primary health care (Subramani et al. 2017).

Despite the fact that traditional medicinal plants have been established through empirical practices and evidences, their importance have often been undervalued and disregarded (Kaliyaperumal et al. 2013). It is estimated that only less than 10% of the world's medicinal plant biodiversity has been scientifically studied for their potential pharmacological activities (Dias et al. 2012). The awareness of medicinal plants and their ethnopharmacological relevance is crucial to discover novel plant-based drugs and medicines, as well as in disease prevention (Sofowora et al. 2013; Jamshidi-Kia et al. 2018). Plants with ethnopharmacological practices have become the main sources of pharmaceuticals in early drug discovery. Therefore, efforts must be directed towards measures that will improve the efficacy, effectiveness, and rational use of medicinal plants (Veeresham, 2012; Sofowora et al. 2013).

Among the traditional medicinal plants, members of Mahogany or Meliaceae family have been regarded for their medicinal properties. This family consists of approximately 1400 species belonging to more than 50 genera. Modified triterpene compounds called Limonoids are abundantly found in Meliaceae and are chemically more diverse in this family compared to any other plant families (Paritala et al. 2015). A large quantity of other triterpenoid derivatives as well as other compounds such as flavonoids, alkaloids, phenols, coumarins, lignans, and chromones are also present in different Meliaceae genera (Paritala et al. 2015; Yadav et al. 2015). These very diverse compounds are responsible for the wide range of medicinal properties of Meliaceae such as antiviral, antiparasitic, and antimicrobial activities, as well as cytotoxic, anticancer, and anti-inflammatory properties (Paul et al. 2011;

Xavier-Jr et al. 2015; Yadav et al. 2015; Mubeen et al. 2018). The members of this family have been traditionally used for treating a wide range of diseases (Sujarwo et al. 2016; Agyare et al. 2018).

Among the Meliaceae family, only a few members have edible fruits, in which *Sandoricum koetjape* (Burm.f.) Merr. is one of the most popular species (Yadav et al. 2015). The species *S. koetjape* belongs to genus Sandoricum Cav, that is distributed mainly in tropical areas in Asian countries and among plant that have been utilized for traditional medicines (Ismail et al. 2003a). The root, bark, leave, and the whole plant of *S. koetjape* are used in folk medicine for generations in some Asian countries such as India, Malaysia, Indonesia, and Thailand for treating various diseases such as diarrhea, leucorrhea, colic, or drunk as a tonic after childbirth (Perry and Metzger, 1980; Kaneda et al. 1992; Ismail et al. 2003a). A number of phytochemicals and bioactive compounds from *S. koetjape* have been identified and tested *in vitro* which showed large therapeutic potentials (Ismail et al. 2003a; Aisha et al. 2009a, b; Chudzik et al. 2015;).

This review aims to comprehensively integrate current knowledge on *S. koetjape* by focusing into three main aspects namely ethnomedicinal, phytochemistry, and pharmacology. Moreover, we discussed toxicological aspects that have not been studied from *S. koetjape* and some issues to translate the therapeutic capacity of this plant into consumable product.

BOTANY AND ETHNOMEDICINAL ASPECTS OF *Sandoricum koetjape*

S. koetjape is possibly indigenous plants of Indochina and Peninsular Malaysia, and later the plant has been introduced and naturalized in the Philippines, Borneo, Indonesia, India, the Andaman Islands, Mauritius, Australia, Taiwan, China, and also into a few other locations in Southern Florida and Central America (Lim, 2012). *S. koetjape* is locally called kechapi, lolly fruit, santol, sentol, wild mangosteen (English), faux mangostan, and sandorique mangousteiner savage (French). This plant is classified into the genus Sandoricum, of the Meliaceae family, order Sapindales, and division Tracheophyta (Barstow, 2018). Other synonymies for *S. koetjape* are *Melia koetjape* Burm.f., *Sandoricum indicum* Cav., *Sandoricum maingayi* Hiern, *Sandoricum nervosum* Blume, *Sandoricum nervosum* (Vahl) M.J. Roem., *Sandoricum vidalii* Merr., *Trichilia nervosa* Vahl (Lim, 2012; Mabberley, 1985).

Distribution of *S. koetjape* is mainly in primary and secondary rain forests below 1000 m which are characterized by deciduous, small to large tree, up to 50 m tall with a straight trunk, flaky or fissured, lenticillate, greyish to pale pinkish-brown bark (Orwa et al. 2009; Lim, 2012). The tree bole morphology of *S. koetjape* is straight but often crooked or fluted, branchless for up to 18–21 m and with a trunk diameter up to 100 cm (Lim, 2012). Bark surface smooth or sometimes flaky or fissured, lenticillate, greyish to pale pinkish-brown, inner bark pale brown or red-brown to pink, exuding a milky latex (Orwa et al. 2009). It produces fleshy fruits that are round or flattened ball-shaped, yellow or brownish, and 5-8 cm across, with arils part range from sour to sweet (Figure 1) (Chen et al. 2015). The fruit has 3 - 5 brown, ovate to ellipsoid seeds, 2–3.5 by 1.2–2.1 by 0.9–1.6 cm, which are usually tightly associated to the pulp (Chen et al. 2015).

Figure 1. *Sandoricum koetjape* fruits.

Traditionally, *S. koetjape* has been applied as medications to treat a number of diseases in Thailand, Malaysia, Philippines, and Indonesia. In Thailand, this plant is locally known as *krathon* or *sathon* and its bark decoction is traditionally used to treat diarrhea (Kaneda et al. 1992). Meanwhile, the aqueous extract of *S. koetjape* or *santol* bark in Malaysia is consumed after childbirth as a tonic (Nassar et al. 2010). Moreover, the stem bark of *S. koetjape* or locally called *sentul* or *kecapi* in Indonesia is used by local people for colic, leucorrhoea, and stomach ache treatment (Kosela et al. 1995; Novaryatiin and Indah, 2019). Moreover, the pounded bark is applied for treating ringworm (Perry and Metzger, 1980).

Beside the bark, other plant parts of *S. koetjape* such as leaves and roots are also conventionally used for several diseases treatments. Decoction of the leaves of *S. koetjape* is being used to treat diarrhea and water from the pounded leaves is used as intermittent fever medication (Perry and Metzger, 1980). In the Philippines, fresh leaves of *S. koetjape* are put on the body to induce sweating while santol herbal tea is used

to bath to bring down fever (Lim, 2012). The leaves are also used for inflammation or swelling poultice by applying directly to the affected area (Agapin, 2020). The root is used to cure leucorrhoea, dysentry, and as general tonic (Perry and Metzger, 1980). The decoction or infusion of *S. koetjape* roots is also used for diarrhea and spasm treatment (CABI, 2008). A record of Balinese traditional healing therapies written in palm leaves called Taru Pramana stated that "loloh" or traditional herbal drink of *S. koetjape* roots and leaves is employed to treat diarrhea, while the bark can be chewed and then sprayed into the stomach (Pulasari, 2013). The bark and leaves of *S. koetjape* are also used in treating diarrhea by the Baduy Ethnic in Indonesia (Khastini et al. 2021).

PHYTOCHEMICALS OF *Sandoricum koetjape*

The phytochemicals constituent of *S. koetjape* has been examined since 1960. To date, more than 30 compounds have been isolated from different parts of this plant, in which triterpenes are the ubiquitous plant components. Various group of triterpenes were identified in this plant such as Ring-A secotriterpene, oleane-type triterpene, secomultiflorane-type triterpene, hydroxy-multiflorane triterpene, and limonoids. Besides, sesquiterpenes and polyalcohols were also detected in stem and fruit hulls of *S. koetjape*. Polyphenols such as quercetin (flavonoid) and tannin were also observed in the plant extracts of *S. koetjape* (Table 1).

Table 1. Compounds identified from the *Sandoricum koetjape* extracts.

Class	Compounds	Plant Parts	Ref
Triterpenoind acids	Katononic acid (3-oxo-olean-12-en-29-oic acid)	Stem	(Kaneda et al. 1992)
	Katonic acid (3α-hydroxyolean-12-en-29-oic acid)	Heartwood	(King and Morgan, 1960)
	Indicic acid	Heartwood	(King and Morgan, 1960)
	Bryonolic acid	Fruit hulls	(Sim and Lee, 1972)
Ring-A secotriterpene	Koetjapic acid	Stem	(Kaneda et al. 1992)
	Sentulic acid	Bark	(Efdi et al. 2012)
Oleane-type triterpenoid	3-oxo-olean-12-en-27-oic acid	Bark	(Efdi et al. 2012)
	20-epikoetjapic acid (3,4-seco-olean-4(23),12-diene-3,29-dioic acid)	Stem bark	(Tanaka et al. 2001)
	3-epikatonic acid	Stem bark	(Tanaka et al. 2001)
	Briononic acid	Stem bark	(Tukiran et al. 2010)
Secomultiflorane-type triterpene	Bryononic acid	Fruit hulls, stem bark	(Sim and Lee, 1972; Kosela et al. 1995)
	Secobryononic acid	Stem bark	(Kosela et al. 1995)
	Secoisobryononic acid	Stem bark	(Kosela et al. 1995)
12β-hydroxymultiflorane triterpenoid acid	Sandorinic acid A (12β,18-dihydroxy-3-oxomultiflora-8-en-29-oic acid)	Stem bark	(Tanaka et al. 2001)
	Sandorinic acid B (12β,18-dihydroxy-3-oxomultiflora-7-en-29-oic acid)	Stem bark	(Tanaka et al. 2001)
	Sandorinic acid C (12β-hydroxy-3-oxomultiflora-8-en-29-oic acid)	Stem bark	(Tanaka et al. 2001)
Limonoids/ tetranorterpenoid	[2α-(2-methylbutanoyl)oxy]sandoricin	Leaves	(Pancharoen et al. 2005)
	[2α-(2-methylpropanoyl)oxy]sandoricin	Leaves	(Pancharoen et al. 2005)
	Sanjecumins A and B	Leaves	(Nagakura et al. 2013)
Trijugin-class limonoids	Sandrapins A-C	Leaves	(Ismail et al. 2003b)
	Sandrapins D-E	Leaves	(Ismail et al. 2005)
	Koetjapin D	Seed	(Bumi et al. 2019)
Andirobin-class limonoids	Sandoripin A and B	Leaves	(Pancharoen et al. 2009; Nagakura et al. 2013)
	Sandoricin	Seed	(Powell et al. 1991)
	6-hydroxysandoricin	Seed	(Powell et al. 1991)
	Koetjapins A-C	Seed	(Bumi et al. 2019)
Sesquiterpenes	(–)-alloaromadendrene (–)-caryophyllene oxide (+)-spathulenol	Stem	(Kaneda et al. 1992)
Polyalcohols	Mesoinositol	Fruit hulls	(Sim and Lee, 1972)
	Dimethyl mucate	Fruit hulls	(Sim and Lee, 1972)
Flavonoid	Quercetin	n/d	(Kaewkod et al. 2021)
Tannin	-	n/d	(Kaewkod et al. 2021)

Note: n/d = not determined

PHARMACOLOGICAL ACTIVITIES OF *Sandoricum koetjape*

Antibacterial activity

New antibiotic agents are urgently needed due to high antibiotics resistance incidence worldwide that threaten our action to combat serious bacterial infections (Mayor, 2018). Plants produce a wide range of phytochemicals and secondary metabolites that have therapeutic properties and therefore they are one of the most crucial sources of antimicrobial agents. A study by Subramani and co-workers reported that a total of 60 plant extracts and 110 purified compounds were acquired from 112 plants against multi-drug resistant (MDR) pathogens including MDR-*Mycobacterium tuberculosis*, methicillin resistant *Staphylococcus aureus* (MRSA), and *Plasmodium* spp. between 2005 and 2015 (Subramani et al. 2017).

Plants belong to Meliaceae family have been shown to have antibacterial activity, including *S. koetjape*. A number of antibacterial activities have been documented from this plant (Table 2). Methanol extract of *S. koetjape* seed seems promising as it shows strong antibacterial activity with minimum inhibitory concentration (MIC) at 0.25, 0.50, and 0.50 µg/mL against *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* respectively (Azziz et al. 2013). Meanwhile, the aqueous extract of the seed exhibit weak antibacterial property with MIC at 250 mg mL^{-1} against *Escherichia coli*, *S. aureus*, *Candida albicans,* and *Streptococcus pneumoniae* (Elijah et al. 2016). The observed antibacterial activities in *S. koetjape* could be related to arrays of secondary metabolites such as alkaloids, flavonoids, and phenolic compounds found in this plant. Flavonoid is known by its ability to interact with bacterial membrane proteins, causing the increase in membrane permeability and lead to membrane disruption (Gupta and Birdi, 2017). Terpenoids that ubiquitously present in this plant have been reported to display antibacterial in nature (Gupta and Birdi, 2017).

Table 2. Antibacterial activity of *Sandoricum koetjape* extracts.

Solvents	Suggested Constituents	Property		Target	Ref
		MIC	ZOI		
Seed					
Methanol	Alkaloid, flavonoid	0.25 µg mL^{-1}	-	*B. subtilis*	(Azziz et al. 2013)
		0.50 µg mL^{-1}	-	*P. aeroginosa*	
		0.50 µg mL^{-1}	-	*S. aureus*	
Aqueous	Phenols	250 µg mL^{-1}	-	*E. coli*, *S. aureus*, *C. albicans*, and *S. pneumoniae*	(Elijah et al. 2016)
Leaf					
Aqueous	Phenols	100 µg mL^{-1}	-	*E. coli* and *S. Aureus*	(Elijah et al. 2016)
Fruit juice					
-	Phenols	-	8.3±0.6 mm	*E. faecalis*	(Toobpeng at al. 2017)
		-	13.0±1.0 mm	*P. aeruginosa* MDR1	
		-	14.0±1.0 mm	*E. coli* P174 ESBL	
		-	15.0±0.6 mm	*E. coli* ESBL	
		-	15.0±1.5 mm	*P. aeruginosa* MDR2	
		-	15.0±1.0 mm	*A.Baumannii* MDR2	
		-	15.0±1.5 mm	*A.Baumannii* MDR1	
		-	16.0±1.5 mm	*S. aureus* MRSA1&2	
Fruit hulls					
-	Bryononic acid (triterpenoid)	6 µg mL^{-1}	-	*Salmonella enterica*	(Heliawati et al. 2019)
Root					
Aqueous	n/a	500 µg mL^{-1}	11 mm	*S. pyogenes* NPRC 101	(Limsuwan and Voravuthikunchai, 2013)
Ethanol	n/a	>1000 µg mL^{-1}	15 mm	*S. pyogenes* NPRC 101	
Plant extracts					
Aqueous	Tannin, quercetin (flavonoid)	16 mg mL^{-1}	10.3±0.6 mm	*E. coli* ATCC 25922	(Kaewkod et al. 2021)
		63 mg mL^{-1}	10.3±0.6 mm	*E. coli* K-12	

Note: n/a = not available; MIC = minimum inhibitory concentration; ZOI = zone of inhibition

Anticancer/antitumor activity

S. koetjape is known to be rich in triterpene compounds. In recent years, triterpenoids-related studies show that these compounds have potential roles for tumor or cancer prevention and treatments (Gill et al. 2016; Patlolla and Rao, 2012). Although many triterpene compounds have been proven to give effective results in treating cancers, only some of them have passed the

clinical trial (e.g. 12-dioxooleana-1,9(11)-dien-28-oic acid or CDDO) (Gill et al. 2016).

A number of triterpenoids isolated from *S.koetjape* such as katonic acid, sandorinic acid A, sentulic acid, and koetjapic acid have been noted to have cytotoxic activity against leukemia, colon, and breast cancer cell lines (Table 3) (Kaneda et al. 1992; Tanaka et al. 2001; Efdi et al. 2012; Nassar et al. 2012a). Koetjapic acid has also shown to have cancer chemopreventive and antitumor properties, as well as antimetastatic and antiinflamation activities (Ismail et al. 2003a; Rasadah et al. 2004; Nassar et al. 2012b).

Table 3. Anticancer and antitumor Activity of *Sandoricum koetjape* extracts.

Type of Extracts	Suggested Constituents	Dosage/Results	Ref
Seed			
Methanol	Koetjapin D	Cytotoxic activity against murine leukemia P-388 cell lines with IC^{50} of 16.8 ± 1.8 µg/ml	(Bumi et al. 2019)
Stem			
Diethyl ether	1) 3-oxo-olean-12-en-29-oic acid 2) Katonic acid	Cytotoxic activity against P-388 leukemia cells (ED_{50} 0.61 µg/ml (1) and 0.11 µg/ml (2))	(Kaneda et al. 1992)
Bark			
Purified compounds	1) Sentulic acid 2) 3-oxo-olean-12-en-27-oic acid	Cytotoxic activity against human promyelocytic leukemia HL-60 cell line by inducing apoptosis	(Efdi et al. 2012)
Hexane	Koetjapic acid	Cancer chemopreventive. Significantly delayed tumor promotion in two-stage mouse skin carcinogenesis	(Ismail et al. 2003a)
Hexane	1) Koetjapic acid 2) 3-oxo-olean-12-en-29-oic acid 3) Katonic acid	Anti-tumor promoting agents. Inhibit Epstein-Barr virus early antigen (EBV-EA) activation	(Ismail et al. 2003a)
Stem Bark			
Purified compound	Sandorinic acid A	Cytotoxic activity against human leukemia HL-60 cells (IC_{50} 15 µg/ml)	(Tanaka et al. 2001)
N-hexane	n/a	IC_{50} values of 23, 14, 50, and 52 µg/ml against Human Umbilical Vein Endothelial Cell (HUVEC), human colon cancer cells HCT-116 and HT-29, and normal cell line CCD-18CO	(Aisha et al. 2009b)
N-hexane	n/a	50 µg/ml extract showed potent apoptotic cell death induction on HCT-116 colon cancer cell by inducing caspases 3 and 7 activity	(Aisha et al. 2009b)
Purified compound	Koetjapic acid	Cytotoxic activity with IC_{50} value of 18.88 µg/ml against HCT-116 colon cancer cells by inducing caspase-3/7, -8, and -9, inducing morphological changes and nuclear condensation, causing DNA fragmentation, disrupting mitochondrial membrane potential, down-regulating Wnt, HIF-1α, MAP/ERK/ JNK, and Myc/Mac signalling pathways, up-regulating NF-κB signalling pathway	(Nassar et al. 2012a)
Synthetic	Potassium koetjapate (salt form of koetjapic acid)	Enhanced cytotoxicity against HCT-116 cells compared to koetjapic acid	(Jafari et al. 2014)
N-hexane	n/a	IC_{50} values between 44 – 48 µg/ml against breast cancer cells MCF-7, MDA-MB-231, and T47D, and normal cell line MCF-10A	(Aisha et al. 2009a)
N-hexane	n/a	100 µg/ml extract showed apoptotic cell death induction on MCF-7 breast cancer cell by inducing caspases 3 and 7 activity	(Aisha et al. 2009a)
Methanol	Koetjapin D	Cytotoxic activity against murine leukemia P-388 cell lines with IC^{50} of 16.8 ± 1.8 µg mL^{-1}	(Bumi et al. 2019)
Purified compound	Koetjapic acid	Cytotoxic activity with IC_{50} value of 68.88 µg/ml against MCF-7 breast cancer cells; significantly inhibit cell migration and invasion at 15 µg/ml (sub-toxic dose); significantly inhibit the colony formation properties of MCF-7	(Nassar et al. 2012b)

Other activities

Triterpenes such as koetjapic acid, katonic acid, and 3-oxo-olean-12-en-29-oic acid are found to inhibit DNA polymerase β (Sun et al. 1999; Hu et al. 2004). The mentioned compounds and sentulic acid are also known to have antiinflammation properties (Rasadah et al. 2004; Itoh et al. 2018;).

Limonoids compounds isolated from *S. koetjape* leaves namely sandoripins A and B exhibit antioxidant activity by inhibiting NO production in J774.1 cell line

(Nagakura et al. 2013). In addition, phenolic content and flavonoid from *S. koetjape* fruit extract show antioxidant activity by decreasing ROS production and increasing antioxidant enzyme GPx-1 (Anantachoke et al. 2016). Tannins extracted from methanolic extract of the stem bark also display radical scavenging activity (Cavin et al. 1999). Beside aforementioned pharmacological activities, *S. koetjape* extracts also show antiangiogenic, antifungal, antifeedant, ichthyotoxic, and insecticidal against lepidopteran larvae (Tabel 4) (Mikolajczak and Reed, 1987; Powell et al. 1991; Cavin et al. 1999; Ismail et al. 2003a; Leatemia and Isman, 2004;).

Table 4. Other activities of *Sandoricum koetjape* extracts.

Bioactivities	Extract/ Constituents	Dosage/Results	Ref
Seed			
Antifeedant	Ethanol, hexane	Ethanol and hexane extracts strongly inhibited feeding and resulted in high mortality (feeding ratio 0.05 and 0.21; mortality 90 and 100% respectively) of fall armyworm, *S. frugiperda*	(Mikolajczak and Reed, 1987)
	Sandoricin and 6-hydroxysandoricin	100% effective against larvae of *Spodoptera frugiperda* and *Ostrina nubilalis* at 200 ppm or above.	(Powell et al. 1991)
Insecticidal	Ethanol	Ineffective (49-97% larval growth – relative to control)	(Leatemia and Isman, 2004)
Leaves			
Antioxidant	1) Sandoripins A 2) Sandoripins B	Inhibit NO production with IC_{50} of 16.4 µM (1) and 30.4 µM (2) in mouse macrophage-like J774.1 cells stimulated by LPS	(Nagakura et al. 2013)
Fruits			
Antioxidant	Phenolic content, flavonoid	1 mg/ml extract shows DPPH scavenging activity of 84.73% (IC_{50} of 415.8 µg/mL); supressed ROS production that induced by H_2O_2; significantly increase the protein level of an antioxidant enzyme GPx-1 in human embryonic kidney HEK-293 cell line	(Anantachoke et al. 2016)
Bark			
Ichthyotoxic	1) Koetjapic acid 2) 3-oxo-olean-12-en-29-oic acid	Ichthyotoxic activity with TL_m of 1.8 and 1.9 ppm respectively for compounds 1 and 2	(Ismail et al. 2003a)
Stem			
Anti-inflammation	1) 3-oxo-olean-12-en-29-oic acid; 2) Katonic acid 3) Koetjapic acid	Oedema inhibition of 94% (crude methanolic extract); 100% (dichloromethane fraction); 90% (hexane fraction); 77% (methanol fraction); 64% (ethyl-acetate fraction); 14% (water fraction); 94% (1); 81% (2); 13% (3)	(Rasadah et al. 2004)
Stem Bark			
Anti-inflammation	Sentulic acid (purified compound)	reduced the production of nitric oxide after co-stimulation with LPS/IFNγ in RAW264.7 cell line by inhibiting the binding of LPS to TLR4f	(Itoh et al. 2018)
Antioxidant	Tannins	Show radical scavenging activity against DPPH radical	(Cavin et al. 1999)
Antifungal	1) Dichloromethane extract 2) Methanol extract	Active against *Candida albicans* (1) and *Cladosporium cucumerinum* (2)	(Cavin et al. 1999)
Anti-angiogenic	N-hexane and methanol extract	N-hexane and methanol extracts showed 97% and 90% blood vessel outgrowth inhibition using rat aortic ring assay	(Aisha et al. 2009c)
	N-hexane extract	100 µg/ml extract showed 94±5.5% blood vessel outgrowth inhibition using rat aortic ring assay; and IC_{50} values of 23, 14, 50, and 52 µg/ml against Human Umbilical Vein Endothelial Cell (HUVEC), human colon cancer cells HCT-116 and HT-29, and normal cell line CCD-18CO	(Aisha et al. 2009b)
	Koetjapic acid (purified compound)	20 µg/ml and 40 µg/ml koetjapic acid in ethanol showed 50% and 100% vascularitation inhibition using rat aortic ring assay; non-cytotoxic against HUVECs (IC_{50} 40.97 ± 0.37 µg/ml)	(Nassar et al. 2011)
	Potassium koetjapate (salt form of koetjapic acid)	Supressed angiogenesis by inhibiting endothelial functions and expression of angiogenic cytokine VEGF	(Jafari et al. 2020)
Stem bark and wood			
DNA Polymerase β inhibitor	1) 3-oxo-olean-12-en-29-oic acid 2) katonic acid 3) koetjapic acid	IC_{50} values of 22, 36, and 20 µM for DNA polymerase β inhibitors compounds 1-3 respectively	(Hu et al. 2004; Sun et al. 1999)

Drawbacks and future direction of research

Many studies on antibacterial activity screening of *S. koetjape* were mostly carried out using crude extracts. The results seem promising, but nevertheless has limited impact on further drug development since crude extracts contain many types of compounds with different activities, side effects, as well as toxic effects. Researches related to antitumor and anticancer activity of *S. koetjape* are generally more focused on a specific compound which would be more convenient to be developed into further step in drug development. A milestone in developing a new therapeutic agent from *S. koetjape* has been reached by Jafari and co-workers (2020). Their research chemically modifies the poorly soluble koetjapic acid into more soluble form namely potassium koetjapate, and thus enhanced its antiangiogenesis efficacy in rats. In the future, research about discovering medicinal properties of *S. koetjape* should be focus more on a single compound, rather than the whole extract. Further preclinical and clinical research are also needed to develop the promising compounds contained in *S. koetjape* as new therapeutic agents against a wide range of diseases.

CONCLUSIONS

In conclusion, phytochemicals of *S. koetjape* have been reported to have promising bioactivities that can potentially be used for therapeutic applications. However, more knowledge is required regarding to mode of actions, biosynthetic pathways, and toxicological aspects of these identified compounds. Importantly, many of reported bioactivities were conducted *in vitro*, while compelling evidence of the application of such compounds from *in vivo* studies are rather limited. Toxicological aspects are especially the utmost important particularly to determine the limit concentrations that are safe to be applied to treating such diseases.

***Acknowledgements*:** We would like to thank the Faculty of Medicine and Health Sciences, Warmadewa University, Bali-Indonesia for providing financial support for this study.

***Competing interests*:** The author declares that there are no competing interests.

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