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The Potency of the Genus Uncaria from East Borneo for Herbal Medicine Purposes: A Mini-review

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Abstract

Uncaria is a genus of plants that are widely distributed in the tropics. There are about 5 of the 38 species of this genus growing in the tropical rain forests of East Borneo, Indonesia. For a long time, Uncaria is commonly used as a traditional medicine to treat various diseases by the Dayak tribe in Kalimantan, traditional people believe that Uncaria may be cured cancer, tumors, mioms, and cycts. Based on previous studies, the activity of the genus Uncaria has been widely reported such as cytotoxic, antimicrobial, antioxidant, antidiabetic, and thrombolytic activities. This article aims to summarize the potential of the Uncaria genus, focusing on 5 species from East Borneo, namely *Uncaria nervosa, Uncaria longiflora, Uncaria gambir, Uncaria tomentosa* and *Uncaria cordata*. The method used in this article is a literature study by collecting previous research articles related to the Uncaria genus. The results of the literature study show that the Uncaria genus in East Borneo has many secondary metabolites with diverse chemical structures that show good biological potential so that they can be used as broad and promising insights for drug discovery and development. This paper is also expected to provide input for the policy of conservation of medicinal plants in the forests of East Borneo.

Keywords: Uncaria, Biological activities, herbal medicine, East Borneo plant

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1 Introduction

The tropical rain forests of East Borneo–Indonesia are well known as one of the highest biodiversity areas in the world. Many species of medicinal plants grow in this area, including the *Uncaria*. *Uncaria*, a polytypic genus of Rubiaceae, consists of 38 species worldwide which are distributed in tropical regions in Asia-Pacific [1,2]. Among them, 5 species are found in the tropical rain forests of East Borneo, such as *Uncaria cordata* (Lour.) Merr., *Uncaria longiflora*, *Uncaria gambir* Roxb., *Uncaria nervosa* and *Uncaria tomentosa* [1,2,3,4,5]. Interestingly, the genus *Uncaria* is the most common tropical plant, which has good potency and promising to develop for herbal medicine purposes [6,7,8]. In Indonesia, many species of this genus are commonly used by the Dayak tribe as a folk medicine to combat cancer, diabetes mellitus, rheumatic, asthma, and neurodegenerative disease for a long time [8].

Recently, many previous investigations of the genus Uncaria have been conducted as a scientific basis to prove this traditional usage and they have reported exhibiting various pharmacological effects. Although, much literature on the genus Uncaria has been published, this review focuses on the five Uncaria species which are found in the East Borneo region, such as *Uncaria cordata* (Lour.) Merr., *Uncaria longiflora*, *Uncaria gambir* Roxb., *Uncaria nervosa* and *Uncaria tomentosa*. Their phytochemistry constituent and pharmacological aspects with the possible mechanism of action are also discussed in this article to introduce the potency of this genus and being as theoretical support for the discovery and development of the local Uncaria plants as herbal medicine to prevent and/or treat many pathological conditions in the world people.

2 Reviews

Some excellent reviews of various aspects of the Uncaria study are listed here. An overview of the distribution of secondary metabolites and activities in the genus Uncaria.

3 Phytochemistry

Nowadays, the identification of secondary metabolite of the plant still being a major focus in drug discovery and development, including in the Uncaria plants. Many phytochemistry studies have been conducted to extensively explore the bioactive compounds of this genus. In the last two decades, at least 36 of 97 reported compounds were isolated and identified in the 5 East Borneo species [1,2,3,4,5] and then we clustered them on the basis of their chemical structure as shown by Figure 1.

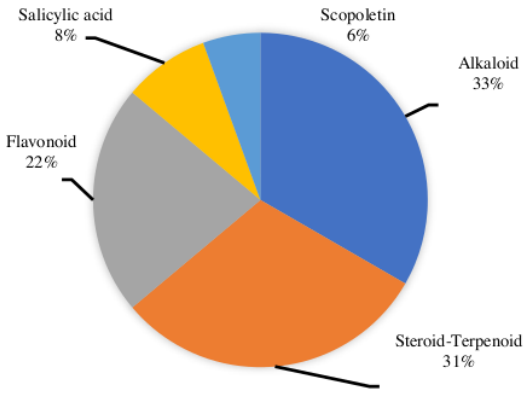

Figure 1. Chemical structure classes of an isolated compound in the 5 East Borneo species of Uncaria genus published from 2000 to 2020. Among them, the alkaloid and steroid-terpenoid groups are the most frequently isolated and identified compounds in these species.

3.1 Alkaloid

Alkaloid was the first major compound group of the Uncaria genus. At least 12 compounds have been isolated from this genus, such as longiflorin (1), isoformosaninol (2) and

formosaninol (3) from *Uncaria longiflora* and dihydrocorynantheine (4), corynoxine (5), corynoxine-B (6), 3-epi-yohimbine (7), rhynchopylline (8), isorhynchopylline (9), uncarine A (10), uncarine D (11), hirsutine (12) from *Uncaria cordata* and *Uncaria nervosa.* 3,4-dehydro-5(*S*)-carboxystrictosidine (13), (5*S*)-carboxystrictosidine (14) from *Uncaria tomentosa* [6,9,10,11,12]. The chemical structures are based on the functional group presented in Figure 2.

3.2 Steroid-terpenoid

The second major compound group of *Uncaria* genus was steroid-triterpenoid group, they were loganin (15) and ß-sitosterol (16) from *Uncaria cordata.* 3*β*,19*α*,23-trihydroxy-6-oxo-olean-12-en-28-oic acid (17), 3*β*-*O*-*β*-*D*-fucopyranosyl-28-*O*-*β*-*D*-glucopyranosyl ester (18), 3*β*-*O*-*β*-*D*-glucopyranosyl-(1→4)-*β*-*D*-fucopyranoside (19), 3*β*-*O*-*β*-*D*-glucopyranosyl-(1→4)-*β*-*D*-fucopyranosyl-28-*O*-*β*-*D*-glucopyranosyl ester (20), 3*β*,19*α*-dihydroxy-6-oxo-urs-12-en-23-al-28-oic acid (21), 3*β*,19*α*-dihydroxy-6-oxo-urs-12-en-23-ol-28-oic acid (22) and tomentosides A (23) were also isolated from *Uncaria tomentosa* [10,11,13] with the chemical structure on the Figure 3.

3.3 Flavonoid

The flavonoid group such as, quercetin (24), kaempferol (25), taxifolin (26), gambirflavan D1 (27), gambirflavan D2 (28), gambirflavan D3 (29), gambirflavan D4 (30) and catechin (31) were identified from *Uncaria cordata* and *Uncaria gambir,* respectively [13,14]. The structures are presented on Figure 4.

3.4 Salicylic acid

2-hydroxybenzoic acid (32), 2,4-dihydrobenzoic acid (33), and 3,4-dihydrobenzoic acid (34), the salicylic acid group (Figure 5), were obtained from *Uncaria cordata* [13].

3.5 Scopoletin

7-hydroxy-6-methoxycoumarin (35) and 3,4-dihydroxy-7-methoxycoumarin (36) belong to scopoletin (Figure 6) were reported as the minor compound group from *Uncaria cordata* [13].

4 Biological activity

Recently, many studies have been conducted for several biological activities evaluation of the extracts and isolated compounds from this genus, and was summarized in Table 1.

Table. 1: Standard deviation and mean for inhibition zones of Carthamus oxycantha against E. coli

S.No	Treatment	Concentration	Zone of inhibition (Mean value)	Standard Deviation (SD)
1	T1	Clindamycin (Standard)	20.00^{b}	1.5275
2	T2	Ampicillin (Standard)	15.00^{c}	1.5275
3	T3	Kanamycin (Standard)	26.00^{a}	1.5275
4	T4	5mg	11.333^{d}	1.5275
5	T5	10mg	12.333^{d}	1
6	T6	15mg	11.333^{d}	1
7	T7	20mg	10.667^{d}	1

LSD value at 0.05 level of significance = 2.3245. Mean followed by the same English letter are not significantly different.

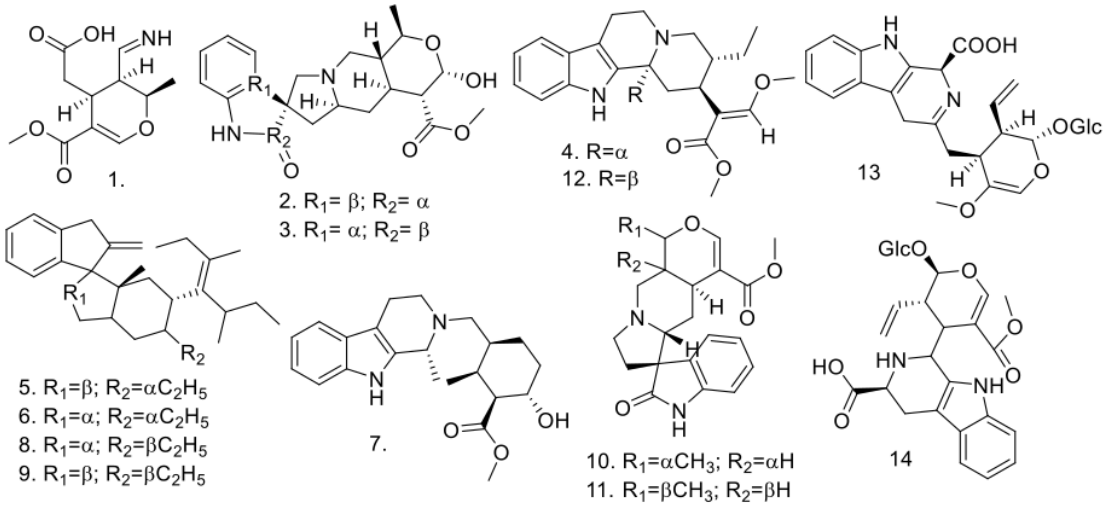

Figure 2. Alkaloid compounds from *Uncaria* genus.

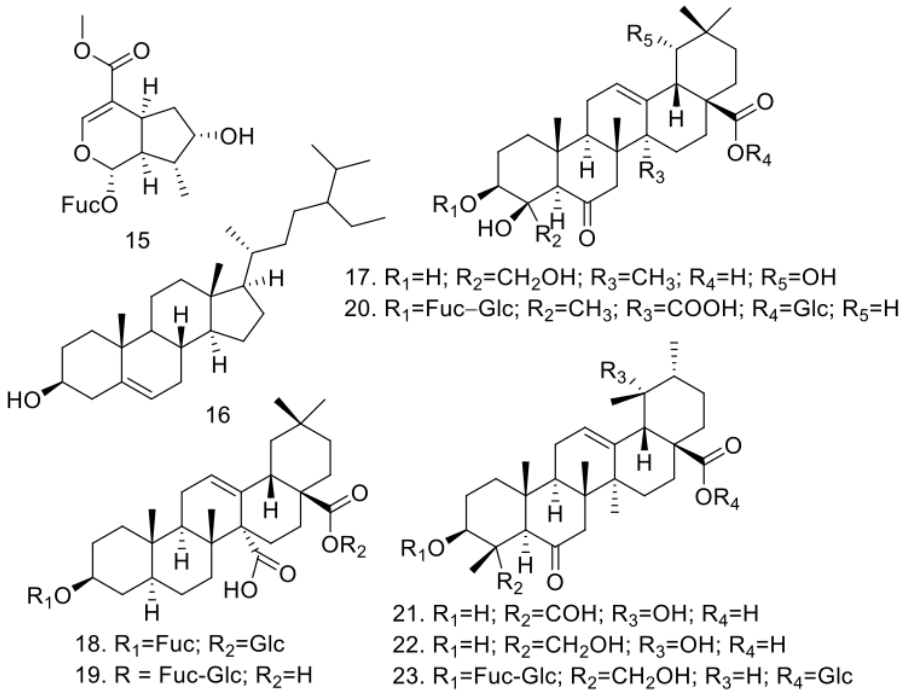

Figure 3. Steroid-triterpenoid compounds from *Uncaria* genus.

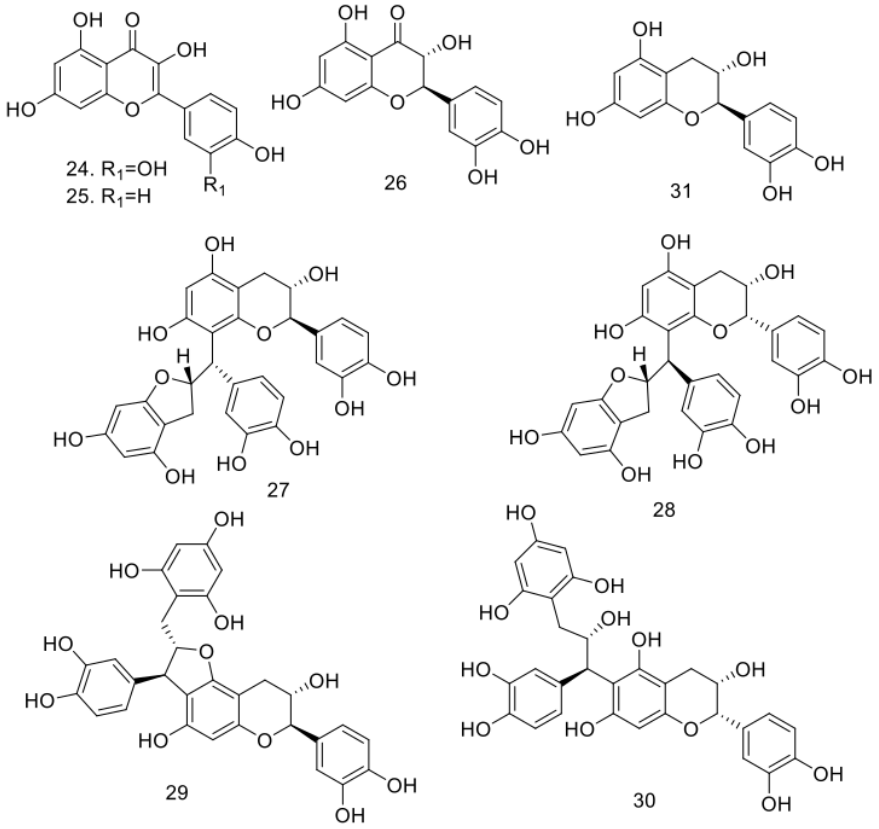

Figure 4. Flavonoid compounds from *Uncaria* genus.

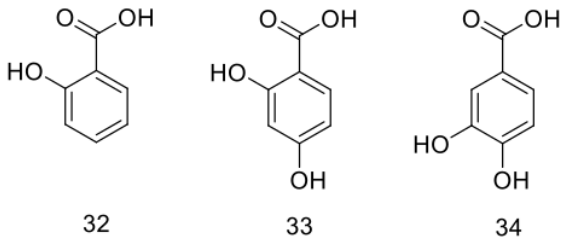

Figure 5. Salicylic acid compounds from *Uncaria* genus.

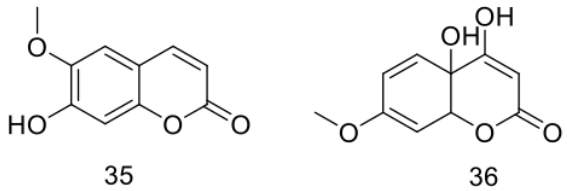

Figure 6. Scopoletin compounds from *Uncaria* genus.

Table 1. The biological activity evaluation of several species of *Uncaria* in the East Borneo

Activity	Experiment	Results	Species	Ref.
Antioxidant	Ethanolic extract was tested using 1.1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging method	Ethanolic extract showed potent antioxidant activity with the 50% inhibition of concentration (IC_{50}) value as much as 13.41 ppm	*Uncaria gambir*	[15]
	Ethanolic extract was tested using lipid peroxidation approach	Ethanolic extract showed more potent anti-lipid peroxidation than α-tocopherol	*Uncaria gambir*	[16]
Analgesic-Antiinflamatory	Catechin was tested by using carrageenan induced paw edema in rats	Catechin (10, 100 mg/kg BW) significantly reduced the edema volume as much as 59.19%	*Uncaria gambir*	[17]
	Ethyl acetate fraction was tested by using carrageenan induced paw edema in rats	Ethyl acetate fraction (5, 10, 20 mg/kg BW) significantly reduced the edema volume as same as diclofenac sodium activity	*Uncaria gambir*	[18]
	The standardized extract in combination with *Morus alba* (1:1) was tested using carrageenan induced inflammation in mice	The extract significantly enhanced the pain resistance, reduced paw edema and ear thickness	*Uncaria gambir*	[19]
	Petroleum eter, chloroform, chloroform: methanol (9:1), methanol and aqueous extract were tested using carrageenan induced paw edema in rats	The chloroform: methanol (9:1) (50 mg/kg BW) and aqueous extracts (84 mg/kg BW) showed the most antiinflammatory activity with the percentage of inhibition of edema as much as 69.2% and 41.2%, respectively	*Uncaria tomentosa*	[20]
Cytotoxic	Ethanolic extract was tested by using brine shrimp nauplii (BSLT assay) and MTT assay on MCF-7 cell line	The ethanolic extract showed the 50% lethal of concentration (LC_{50}) value as much as 361.124 µg/mL on the BSLT assay and decreased the MCF-7 cell viability at the range 20-50% for 10 µM, 40 µM, 70 µM and 100 µM, respectively	*Uncaria cordata*	[21]
	Ethanolic extract was tested using BSLT assay	The extract showed the cytotoxicity potency with the LC_{50} value as much as 21.754 ppm on the death of brine shrimp nauplii	*Uncaria tomentosa*	[22]
	Methanolic extract was tested using BSLT assay	The extract showed a very strong cytotoxic activity with the LC_{50} as much as 1.76 and 2.66 ppm for the bark and wood of the roots, respectively	*Uncaria nervosa*	[5]
	Aqueous extract was tested on the human leukemia cell lines (K562 and HL60) and human EBV-transformed B lymphoma cell line (Raji)	The aqueous extract significantly inhibited the proliferation of HL60, Raji and K562 cells	*Uncaria tomentosa*	[23]
Antimicrobial	10%-ethanolic extract was tested on *Staphylococcus aureus, Escherichia coli* and *Candida albicans* using Kirby-Bauer disk diffusion method	The ethanolic extract inhibited the growth of *Staphylococcus aureus*, but not inhibited on *Escherichia coli* and *Candida albicans*. The zone of inhibition as much as 6.91 ± 0.04 mm, 8.51 ± 0.14 mm and 10.89 ± 1.09 mm at the concentration of 10%, 20% and 40%, respectively	*Uncaria cordata*	[24]
	Micropulverized was tested on the oral clinical isolated microbial strains, such as *Streptococcus mutans, Staphylococcus* sp., *Candida albicans,* Enterobacteriaceae and *Pseudomonas aeruginosa* using Dilution Mueller-Hinton Agar method	The micropulverized inhibited the growth of Enterobacteriaceae, *Streptococcus mutans* and *Staphylococcus* sp., but not inhibited on *Pseudomonas aeruginosa* and *Candida albicans.* The percentage of inhibition as much as 8%, 52% and 96%, respectively at the concentration of 3%	*Uncaria tomentosa*	[25]
	Ointment of ethyl acetate extract was tested using gingival wound rats model	The ointment of ethyl acetate extract significantly decrease the bacterial colonies on the rat's gingival wound in a dose-dependent, 10%, 15% and 20%	*Uncaria gambir*	[26]
	Catechin was tested on the growth of *Streptococcus mutans* using Kirby-Bauer disk diffusion method	Catechin inhibited *Streptococcus mutans* growth at the concentration of 20%, 40% and 80% with the zone of inhibition as much as 0.615 cm, 0.850 cm and 1.085 cm, respectively	*Uncaria gambir*	[27]
	(+)-Catechin and aqueous extract were tested on the growth of *Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus mutans, Streptococcus viridans* and *Bacillus subtilis* using microdilution method	(+)-Catechin inhibited *Staphylococcus epidermidis, Streptococcus mutans* and *Streptococcus viridans* at the concentration of 5.5, 8 and 8 mg/mL, respectively. While > 25 mg/mL to inhibit *Staphylococcus aureus* and *Bacillus subtilis.* In other hand, aqueous extract showed less inhibition potency than catechin with the inhibition concentration as much as 22.5 mg/mL for *Staphylococcus epidermidis* and > 25 mg/mL for the other four bacteria	*Uncaria gambir*	[17]
Trombolytic	Ethanolic extract was tested using the clot lysis of human blood assay method	The extract showed a high trombolytic activity with the percentage of clot lysis as much as 27.36 ± 0.10% at 2 ppm	*Uncaria cordata*	[21]

Table 1. continue

Activity	Experiment	Results	Species	Ref.
Antidiabetic	Ethyl acetate fraction was tested on the *in vitro* α-glucosidase enzyme activity	Ethyl acetate fraction effectively reduced the level of postprandial glucose through the inhibition of α-glucosidase activity	*Uncaria gambir*	[28]
	Aqueous, ethyl acetate and ethanolic extracts were tested on the alloxan-induced diabetic rats	Aqueous, ethyl acetate and ethanolic extracts (100, 200 and 300 mg/kg BW) in 15 days effectively reduced the blood glucose level as much as 27.69%, 38.75% and 50.62%, respectively	*Uncaria gambir*	[29]
Anthelmintic	Ethyl acetate fraction was tested on the Indian adult earthworms (*Pheretima posthuman*)	Ethyl acetate fraction increased in time of paralysis and the time of death of the worms	*Uncaria gambir*	[30]
Antihyperlipidemia	Ethyl acetate fraction was tested on the hyperlipidemic rats model	The administration of ethyl acetate fraction (5, 10 and 20 mg/kg BW) reduced the level of total cholesterol, triglyseride, LDL and increased HDL in the blood plasma	*Uncaria gambir*	[18]

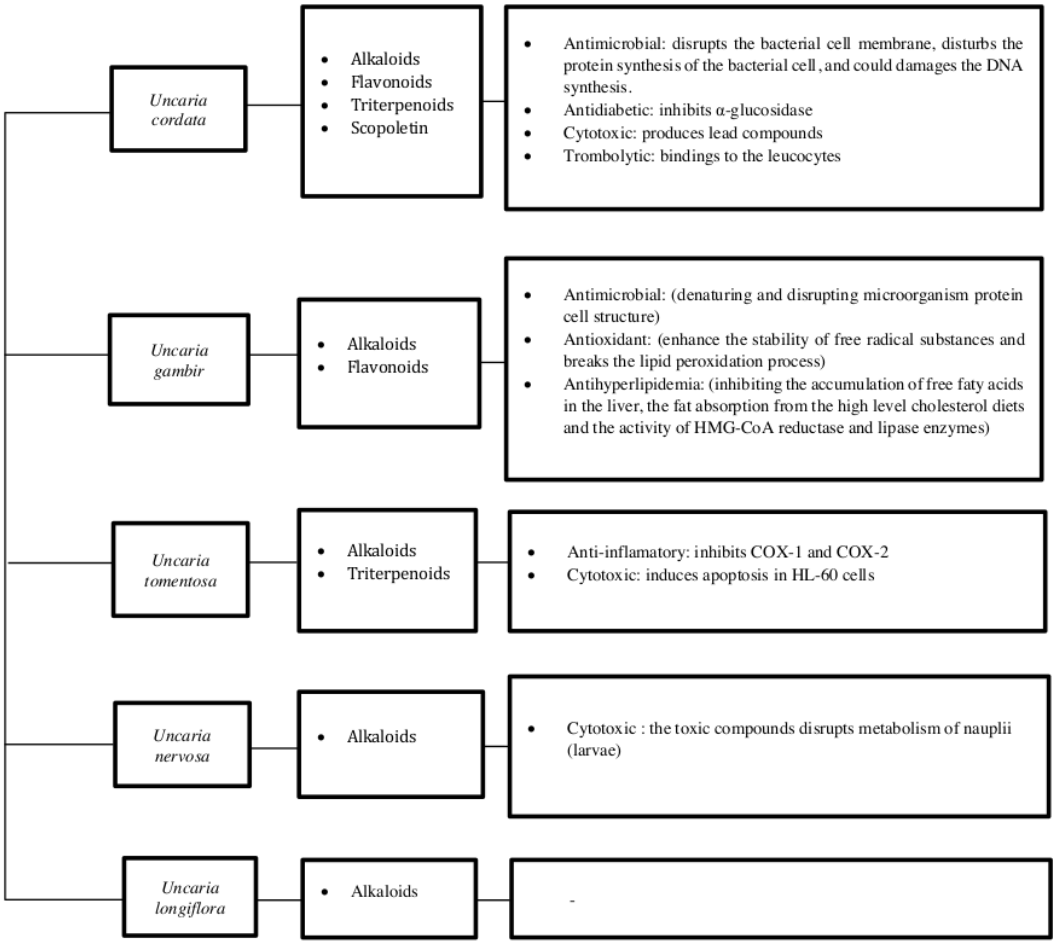

Figure 7. Summarize of compounds, biological activities, and mechanism of biological activity of several Uncaria species in East Kalimantan

Table 1 shows that the crude extract, fraction and isolated compounds from the 5 species of this genus in the East Borneo possess many biological properties, such as antioxidant, analgesic-antiinflamatory, cytoctoxic, antimicrobial, trombolytic, antidiabetic, anthelmintic and antihyperlipidemia with *Uncaria gambir* as the most frequently studied and published, especially in Indonesia and Malaysia, followed by *Uncaria cordata* and *Uncaria tomentosa.*

Moreover, as previously shown in Table 1, the most potential species was represented by *Uncaria gambir*. This plant showed variety of biological properties with several underlying mechanisms. Many literatures have mentioned the potency of this plant strongly associated with its secondary metabolite contents, including catechin. Catechin is a major compound of *Uncaria gambir,* belongs to the flavonoid compound class with various biological actions with a number of established mechanism of actions, such as for antimicrobial, antioxidant and antihyperlipidemia action. For the antimicrobial action, catechin is a toxic substance for bacteria and fungi which effectively inhibited the growth of microorganism by denaturing and disrupting microorganism protein cell structure. This condition lead to increase of the cell membrane permeability and then induces the microbial cell damage. This compound also competitively inhibits the glycosylation process for the formation of extracellular polysaccharide and cause the microbial growth inhibition and death [31]. The antioxidant action of catechin is well correlated to the number of hydroxyl (-OH) moiety of this compound. Hydroxyl (-OH) moiety acts an electron donor to enhance the stability of free radical substances and breaks the lipid peroxidation process [15]. Catechin has also potency as antihyperlipidemia with some mechanism of actions, including by inhibiting the accumulation of free faty acids in the liver, inhibiting the fat absorption from the high level cholesterol diets and inhibiting the activity of HMG-CoA reductase and lipase enzymes, the essential enzyme for the lipid metabolism [18].

Several of the biological activities of the Uncaria genus that have been widely studied. While, the publication of biological activity study for *Uncaria nervosa* and *Uncaria longiflora* is still limited, as shown in Figure 7.

This is an interesting issue for the comprehensive biological potency investigation of these species for the herbal-based drug discovery and development in the further study.

5 Conclusions

Based on the current literature, the five species of *Uncaria* in the East Borneo (*Uncaria nervosa, Uncaria longiflora, Uncaria gambir, Uncaria tomentosa* and *Uncaria cordata*) have many secondary metabolites with the chemical structure diversity that exhibit a good biological potency to develop as antioxidant, analgesic-antiinflamatory, cytoctoxic, antimicrobial, trombolytic, antidiabetic, anthelmintic and antihyperlipidemia. All of the species, *Uncaria gambir* has been the most widely studied and are considered as promising herbs for drug discovery and development.

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7 Conflicts of Interest

The authors declare there is no conflict of interest.

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