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A review on traditional uses, phytochemistry, and pharmacology of the genus *Rourea*

Che Puteh Osman[1*], Zuriati Zahari[1], Mohd Ilham Adenan[1], Rozaini Mohd Zohdi[2]

[1]Faculty of Applied Sciences, Universiti Teknologi MARA, 40450 Shah Alam, Selangor, Malaysia.
[2]Atta-ur-Rahman Institute for Natural Products Discovery, Universiti Teknologi MARA, Selangor Branch, Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor, Malaysia.

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ABSTRACT

Rourea is a genus of climbing shrubs and small trees and widely distributed in the Amazon, Pacific region, Africa, and Asia. It has about 65 species and 129 varieties. They are widely used in ethnomedicine for various health complaints such as rheumatism, diabetes, tumor, asthma, and diarrhea. This paper summarizes 38 compounds from *Rourea* sp. from different classes of compounds such as flavonoids, triterpenes, phenolic compounds, lipids, phytosteroids, and coumarin. Several bioactivities such as hypoglycemia, antinociceptive, antibacterial, antioxidant, antiplasmodial, and larvicidal activities are also discussed.

INTRODUCTION

Rourea is a genus in the Connaraceae family. Genus *Rourea* has about 65 species and 129 varieties (The Plant List, 2013). *Rourea* is a climbing shrub or small tree, usually with prominent lenticels. The leaflets are small and imparipinnate. An unbranched inflorescence bears flowers of five petals in the calyx. They have longer petals than sepals. The fruits are curved and hairless. *Rourea* sp. is widely distributed in the Amazon, Pacific region, Africa, and Asia (Forero, 2009). Some of *Rourea* sp. are poisonous, while others are widely used in traditional medicine. There are several reports on the potential of *Rourea* sp. as hypoglycemic agents. Despite their wide application in ethnomedicine, very few scientific reports on their chemical constituents and biological activity are documented.

*Corresponding Author
Che Puteh Osman, Faculty of Applied Sciences, Universiti Teknologi MARA, 40450 Shah Alam, Selangor, Malaysia.
E-mail: cheputeh @ salam.uitm.edu.my

TRADITIONAL USES

In Malaysia, several *Rourea* species are used by the local communities. The decoction of the roots of *R. regusa* Planch, locally known as *akar semeling*, is traditionally used to treat respiratory diseases (Alsarhan *et al*., 2012). The roots decoction of *R. concolor,* locally known as *akar semelit* in Malaysia, is used by Temuan villagers to treat kidney diseases, diabetes (Ong *et al*., 2011a), lung tumor, and stomach tumor (Ong *et al*., 2011b). *R. mimosoides* or *sembelit merah* is traditionally used to treat bloody diarrhea, as diuretics (Grosvenor *et al*., 1995), and to treat bloody cough (Sabran *et al*., 2016). The roots decoction of *R. humilis* Blume or *akar kayu mengecut* is used to improve the contraction of the uterus (Jamal *et al*., 2011).

R. induta Planch is commonly known as *chapeudinha*, *pau-de-porco,* or *campeira* and is widely distributed in Brazil. It is traditionally used in folk medicine to treat rheumatisms and Chagas disease (Kalegari *et al*., 2014a). *R. cuspidate* Benth ex. Baker is commonly known in Brazil as *miraruíra*, *cip´o miraruíra*, and *muiraruíra*. It is traditionally used to treat diabetes (Laikowski *et al*., 2017).

R. coccinea Benth, commonly known as *Tomigavi,* is used in Togo for the treatment of paralyses and Alzheimer's disease

(Kantati *et al*., 2016). *R. coccinea* is also utilized in Benin traditional medicine for the treatment of male and female infertility, sexual asthenia, blennorrhoea, snakebites, furuncles, and malaria (Bero *et al*., 2009). The leaves of *R. minor* are used as a styptic to treat minor abrasions and lesions in Chinese folk medicine. The stems and roots of *R. minor* are poisonous; however, they are widely used as tying material (He *et al*., 2006). *R. volubis, R. orientalis, R. platysepala,* and *R. glabra* are poisonous and they are often used to deter animals (Jeannoda *et al*., 1985; Oliveira *et al*., 2012). The roots of *R. santaloides* (Vahl.) Wight & Arnott is traditionally taken for the treatment of joint pains and asthma (Bargali *et al*., 2003). *R. puberela* Baker is used in Chazuta Valley of Peruvian Amazon for its diuretic property (Sanz-Biset &Canigueral, 2011).

PHYTOCHEMISTRY

Flavonoids

Isolation from ethanolic leaves extract of *Rourea induta* yielded quercetin **1**, and three glycosylated derivatives, quercetin-3-O-α-arabinofuranoside **2**, quercetin-3-O-β-xyloside **3,** and quercetin-3-O-β-galactoside **4** (Kalegari *et al*., 2011). Procyanidin C1 **5** was isolated from the aqueous leaves extract

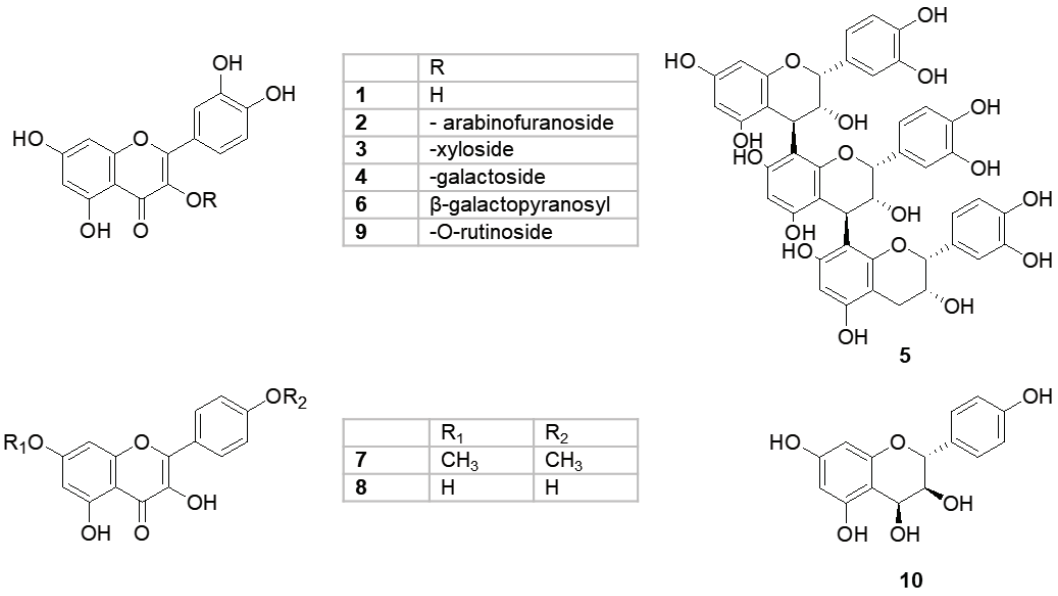


Figure 1. Flavonoids in *Rourea* sp. (Kalegari *et al*., 2011; 2014b; Oliveira *et al*., 2012; Ramiah *et al*., 1976; Zhang *et al*., 2008).

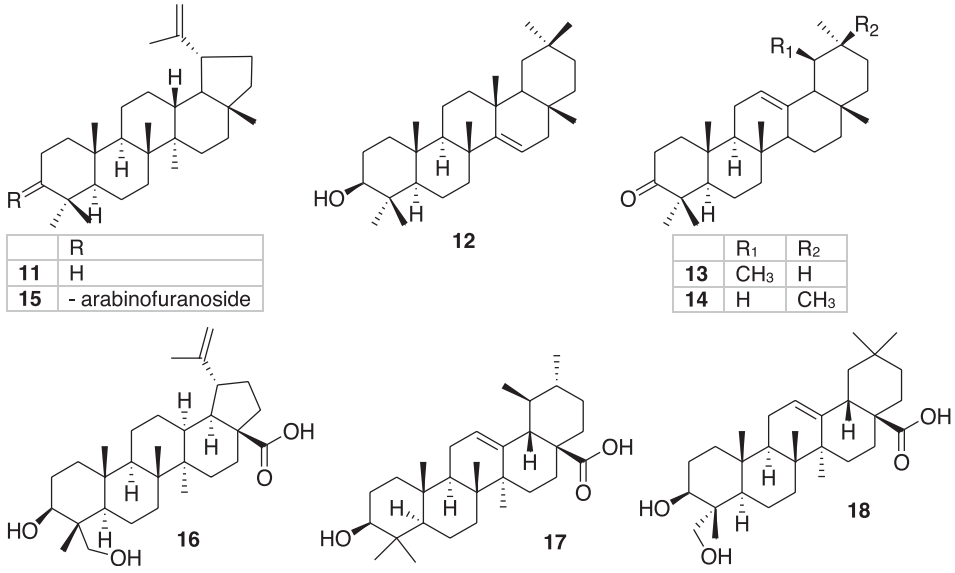
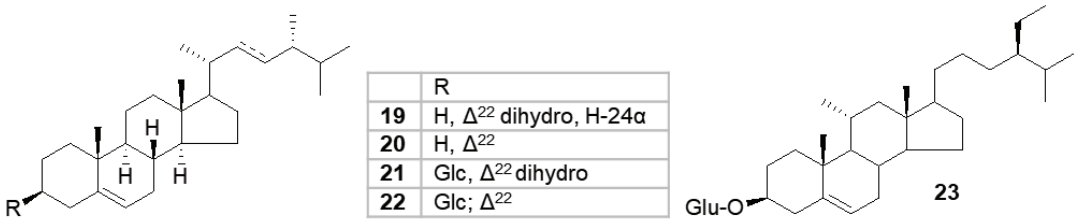
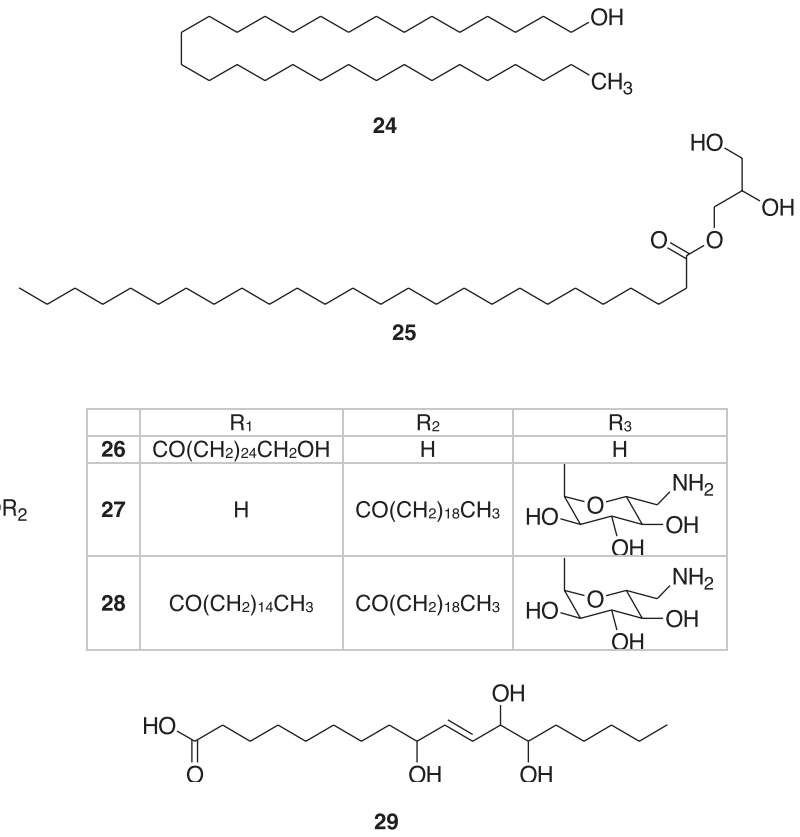


Figure 2. Triterpenes in *Rourea* sp. (Oliveira *et al*., 2012; Zhang *et al*., 2008).



	R
19	H, Δ^{22} dihydro, H-24α
20	H, Δ^{22}
21	Glc, Δ^{22} dihydro
22	Glc; Δ^{22}

Figure 3. Phytosteroids in *Rourea* sp. (He *et al*., 2006; Oliveira *et al*., 2012).



	R_1	R_2	R_3
26	$CO(CH_2)_{24}CH_2OH$	H	H
27	H	$CO(CH_2)_{18}CH_3$	
28	$CO(CH_2)_{14}CH_3$	$CO(CH_2)_{18}CH_3$	

Figure 4. Lipids in *Rourea* sp. (He *et al*., 2006; Zhang *et al*., 2008).

of *R. induta* (Kalegari *et al*., 2014b). HPLC titration of the aqueous leaves extract of *R. induta* revealed the presence of hyperin **6**, as well as compounds **2**–**4** (Kalegari *et al*., 2014b). The phytochemical study on the chloroform fraction of ethanolic leaves extract of *R. doniana* led to the isolation of 7,4'-dimethylkaempferol **7** (Oliveira *et al*., 2012). Kaempferol **8** and rutin **9** were reported in *R. microphylla* (Zhang *et al*., 2008). Leucopelargonidin **10** was isolated from the roots of *R. santoloides* (Ramiah *et al*., 1976).

Triterpenes

Purification of hexane fraction of ethanolic leaves extract of *R. doniana* yielded lupeol **11**, lupenone **12**, α-amyrenone **13**, β-amyrenone **14**, and taraxerol **15** (Oliveira *et al*., 2012). Phytochemical study on *R. microphylla* gave 23-hydroxybetulinic acid **16**, ursolic acid **17,** and hederagenin **18** (Zhang *et al*., 2008).

Phytosteroids

Isolation on chloroform fractions of ethanolic leaves extract of *R. doniana* yielded β-sitosterol **19**, stigmasterol **20**, β-sitosteryl-3-O-β-D-glucopyranoside **21,** and stigmasteryl-3-O-β-D-glucopyranoside **22** (Oliveira *et al*., 2012). β-sitosterol glucoside **23** was isolated from *R. minor* (He *et al*., 2006).

Lipids

1-Hentriacontanol **24** and 1-hexacosanoyl glycerol **25** were isolated from *R. microphylla* (Zhang *et al*., 2008). Isolation on chloroform soluble fraction of methanolic stems extract of *R. minor* gave 1-(26-hydroxyhexacosanoyl)-glycerol **26**, 1-O-ß-D-glucopyranosyl-(2S,3R,4E-8Z)-2-N-(20-hydroxypalmitoyl)-octadecasphinga-4,8-dienine **27**, rourimin **28,** and 9S,12S, 13S-trihydroxy-10E-octadecenoic acid **29** (He *et al*., 2006).

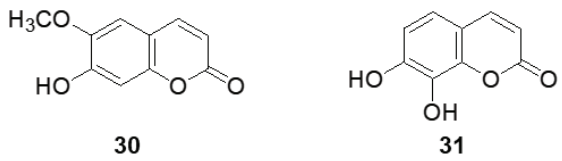


Figure 5. Coumarin in *Rourea* sp. (Oliveira *et al*., 2012; Zhang *et al*., 2008).

Coumarin

Scopeletin **30** was purified from chloroform fraction of ethanolic leaves extract of *R. doniana* (Oliveira *et al*., 2012). Daphnetin **31** was reported from *R. microphylla* (Zhang *et al*., 2008).

Phenolic acid

Purification of the aqueous leaves extract of *R. induta* yielded chlorogenic acid **32** and neochlorogenic acid **33** (Kalegari *et al*., 2014b). (E)-Ferulic acid nonacosyl ester **34** was isolated from *R. microphylla* (Zhang *et al*., 2008).

Others

Purification of hexane fraction of ethanolic leaves extract of *R. induta* yielded n- tetracosane **35** (Kalegari *et al*., 2011). Ropanone **36** was purified from *R. santoloides* (Ramiah *et al*., 1976). Isolation of chloroform soluble fraction of methanolic stems extract of *R. minor* yielded dihydrovomifoliol-9-β-D-glucopyranoside **37** (He *et al*., 2006). Rourinoside **38** was isolated from the chloroform soluble fraction of methanolic stems extract of *R. minor* (He *et al*., 2006).

BIOLOGICAL ACTIVITY

Hypoglycemic activity

Rourea minor

The methanol roots extract of *R. minor* showed antihyperglycemic activity in a dose-dependent manner at 200 and 400 mg/kg when administered to streptozotocin-induced diabetic rats. In oral glucose tolerance test, no glucose lowering effect was observed at 30 and 60 minutes but the effect was quite

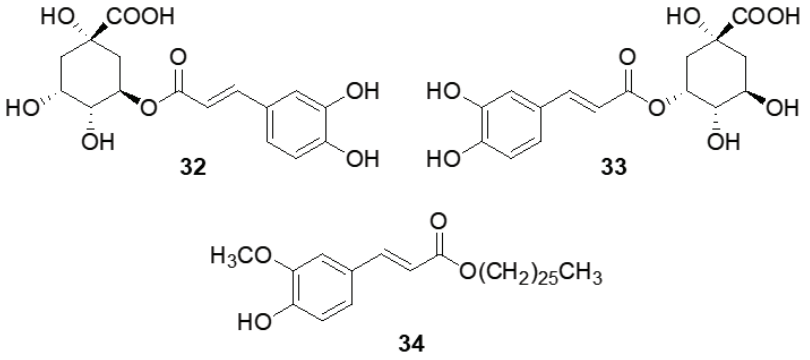


Figure 6. Phenolic acids in *Rourea* sp. (Kalegari *et al*., 2014b; Zhang *et al*., 2008).

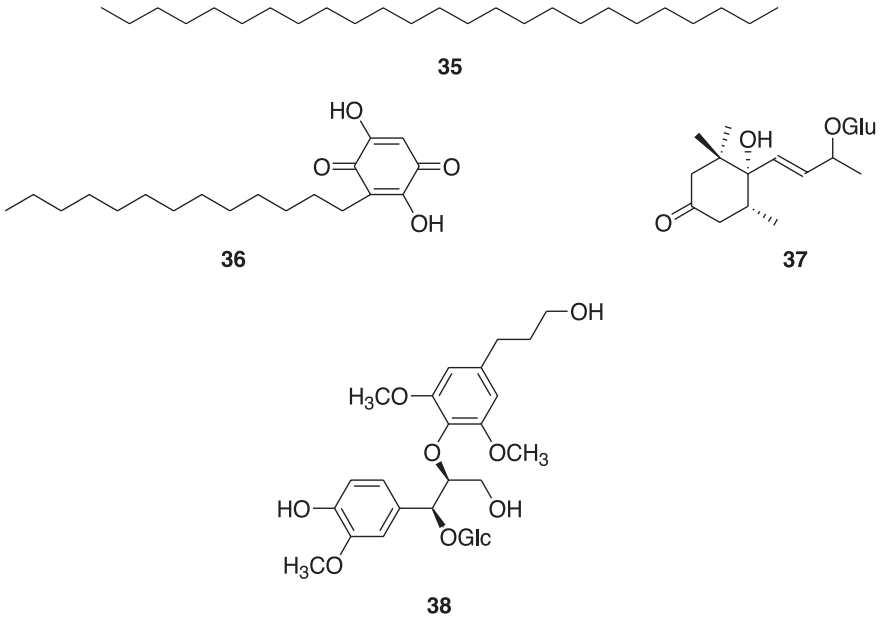


Figure 7. Other compounds in *Rourea* sp. (He *et al*., 2006; Kalegari *et al*., 2011; Ramiah *et al*., 1976).

Table 1. Bioactivities of *Rourea* sp.

Species	Bioactivity	Plant parts	Type of preparation	Main finding
R. minor	Hypoglycemic activity	Roots	Methanol extract	The extracts at all doses are effective in lowering glucose level after 60 minutes in the oral glucose tolerance test. Administration of the extract resulted in a significant reduction of hyperglycemia in dose- dependent manner (Chaudhary *et al.*, 2012).
		Roots	Ethanol and water extracts	Treatment with the extracts reduced glycemia significantly and resulted in higher insulin secretion than the negative control group (Kulkarni *et al.*, 2014).
	Acute toxicity	Roots	Methanol extract	No acute toxicity was observed when rats were given 100, 200, and 400 mg/kg of methanolic extract (Chaudhary *et al.*, 2012).
		Roots	Ethanol and water extracts	The rats showed good tolerance up to 3 g/kg and no lethality was observed (Kulkarni *et al.*, 2014).
	Antiplasmodial activity	Dried vines	Chloroform fraction of methanol extract.	Compounds **38**, **28,** and **26** isolated from *R. minor* showed antiplasmodial activity *in vitro* against chloroquine sensitive (D6) and chloroquine resistant (W6) *Plasmodium falciparum* with the IC_{50} values of about 10 µM (He *et al.*, 2006).
	Hepatoprotective activity	Leaves	Ethanol extract	The extract normalized liver functions and hepatic oxidative stress in CCl_4 treated rats. The endogenous antioxidant defense was restored and lipid peroxidation in the liver was reversed over 7 days' post-treatment with the extract, similar to the effects shown by Legalon (Kalegari *et al.*, 2014b).
	Antinociceptive activity	Leaves	Hot water infusion	Treatment of aqueous extract on mice resulted in the significant antinociceptive effect on different pain models without affecting the motor activity and corporal temperature of the mice, and the extract did not depend on the opioid system (Kalegari *et al.*, 2014a).
R. induta	Acute toxicity	Leaves	Ethanol extract	Ethanolic leaves extract of *R. induta* and its fractions showed no potential toxicity in brine shrimp assay and hemolytic test (Oliveira *et al.*, 2012).
	Antibacterial activity	Leaves	Ethyl acetate and chloroform fractions of ethanol extract	Chloroform and ethyl acetate fractions of chloroform extract showed inhibition against *S. epidermidis* and *S. aureas* (Kalegari *et al.*, 2012).
	DPPH radical scavenging activity	Leaves	Ethyl acetate and chloroform fractions of ethanol extract	The chloroform and ethyl acetate fractions of ethanol leaves extract of *R. induta* showed significant DPPH radical scavenging activity with the IC_{50} values of 5.3 and 3.2 µg/ml, respectively (Kalegari *et al.*, 2012).
	Phosphomolybdenum complex method	Leaves	Ethyl acetate and chloroform fractions of ethanol extract	Hexane, chloroform, and ethyl acetate fractions of ethanolic leaves extract of *R. induta* showed more than 100% activity in relation to rutin and vitamin C (Kalegari *et al.*, 2012).
R. cuspidata	Hypoglycemic activity	Stems	Ethanol and water extracts	Oral administration of hydroalcoholic stems extract of *R. cuspidata* at 200 mg/kg significantly reduced the glucose level in streptozotocin-induced diabetic rats comparable to glibenclamide (Laikowski *et al.*, 2017).
R. doniana	Larvicidal activity	Stems Leaves	Hexane extract	The chloroform leaves extract and hexane stems extract of *R. doniana* caused 88.9% mortality rate of the *Aedes aegyptii* larvae at the concentration of 250 µg/ml (Oliveira *et al.*, 2010).

significant after 90 and 120 minutes administration of the extract. Administration of 100, 200, and 400 mg/kg of methanol extract resulted in a significant reduction of hyperglycemia at days 4, 8, and 12 in a dose-dependent manner. Oral administration of methanol roots extract of *R. minor* at all doses significantly reduced glucose level in the diabetic rats (Chaudhary *et al*., 2012).

In another study, hypoglycemic activity was observed over 120 minutes in streptozotocin-induced diabetic rats treated with ethanolic and aqueous roots extract of *R. minor* at 400 mg/kg as compared to diabetic control rats. After 15 days, treatment with ethanolic and aqueous extracts reduced glycemia significantly at 43.1% and 34.8%, respectively. The diabetic rats treated with ethanol extracts showed higher insulin secretion at 19.7 µU/ml as compared to those treated with water extract, which showed insulin secretion at 17 µU/ml. The insulin secretion of diabetic control rats and glibenclamide treated rats (10 mg/kg) were less than 5 and 22 µU/ml, respectively. Both extracts reversed the elevated lipid parameters and normalized them significantly to near normal values (Kulkarni *et al*., 2014).

Rourea cuspidata

Oral administration of hydroalcoholic stems extract of *R. cuspidata* at 200 mg/kg significantly reduced the glucose level in streptozotocin-induced diabetic rats comparable to glibenclamide. Hydroalcoholic extract contains flavonoids as major compounds. The extract showed a significant hepatoprotective effect on the rat's liver as shown by reduction of AST level from 253 to 49 U/l (Laikowski *et al*., 2017).

Antibacterial activity

The chloroform and ethyl acetate fractions of ethanol leaves extract of *R. induta* showed potential antibacterial activity against *Staphylococcus aureas* and *S. epidermidis* at 1,000 µg/ml. Chloroform fractions showed inhibition against *S. epidermidis* and *S. aureas* with average inhibition halos of 12.3 and 7.6 mm, respectively. Ethyl acetate fraction showed antibacterial activity against *S. epidermidis* and *S. aureas* with average inhibition halos of 15.0 and 7.6 mm, respectively. Antibacterial activity of the ethanol extract could be due to the presence of hyperin **6**,

which showed antibacterial activity against *S. epidermis* at 1,000 and 500 µg/ml with average inhibition halos of 9.3 and 7.0 mm, respectively (Kalegari *et al*., 2012).

Hepatoprotective activity

Administration of 500 mg/kg of ethanolic leaves extract of *R. induta* caused a significant reduction in AST and ALT activities and TB level in the CCl_4 treated group comparable to Legalon. The weight of the liver of the treated group was also smaller as compared to the non-treated control group. Treatment with the extract also normalized the hepatic oxidative stress markers CAT, SOD, GPx, and GSH as compared to the non-treated control group, although Legalon showed a stronger effect. The endogenous antioxidant defense was restored and lipid peroxidation in the liver was reversed over 7 days post-treatment with the extract, similar to the effects shown by Legalon. The hepaprotective activity could be due to the presence of flavonoids **2**, **3,** and **6** (Kalegari *et al*., 2014b).

Antinociceptive activity

Treatment of aqueous leaves extract of *R. induta* on mice showed a significant antinociceptive effect on different pain models without affecting the motor activity and corporal temperature of the mice, and the extract did not depend on the opioid system. The aqueous extract inhibited the neurogenic (0–5 minutes) and inflammatory (15–30 minutes) phases of formalin-induced licking at 30, 100, and 100 mg/kg. The marker compound, hyperin **6,** showed comparable result at 100 mg/kg at the neurogenic phase of the test. The mice in the extract treated group showed a significant reduction (60%–65%) of the mechanical sensitivity on the ipsilateral paw when induced with intraplantar injection of Complete Freund's Adjuvant. The treatment of the extract reduced the level of IL-1β and TNF-α in the skin of the hind paw by 22% and 50%, respectively, as compared to the non-treated control group. The treated group showed a significant reduction in biting behavior caused by TNF-α (0.1 pg/site i.t.) but no effect was observed on IL-1β-induced biting response. It was concluded that the antinociceptive effect of the aqueous leaves extract of *R. induta* is due to decrease synthesis or release of pro-inflammatory cytokines, such as TNF-α and IL-1β (Kalegari *et al*., 2014a).

Antiplasmodial activity

Rourinoside **38**, rouremin **28,** and 1-(26-hydroxyhexacosanoyl)-glycerol **26** isolated from *R. minor* showed antiplasmodial activity *in vitro* against chloroquine sensitive (D6) and chloroquine resistant (W6) *Plasmodium falciparum* with the IC_{50} values of 3.7/2.1 µM, 5.1/4.5 µM, and 9.5/12.7 µM, respectively (He *et al*., 2006).

Larvicidal activity

The hexane stems extract of *R. doniana* showed potential antilarvicidal activity with the LD_{50} value of 12.1 µg/ml. The chloroform leaves extract and hexane stems extract of *R. doniana* caused 88.9% mortality rate of the *Aedes aegyptii* larvae at the concentration of 250 µg/ml (Oliveira *et al*., 2010).

Acute toxicity

No acute toxicity was observed when rats were given 100, 200, and 400 mg/kg of methanolic roots extract of *R. minor* (Chaudhary *et al*., 2012). In other study on ethanolic and aqueous roots extracts of *R. minor*, the rats showed good tolerance up to 3 g/kg and no lethality was observed (Kulkarni *et al*., 2014). Ethanolic leaves extract of *R. induta* and its fractions showed no potential toxicity in brine shrimp assay and hemolytic test (Oliveira *et al*., 2012).

Antioxidant activity

DPPH radical scavenging activity

The chloroform and ethyl acetate fractions of ethanol leaves extract of *R. induta* showed significant DPPH radical scavenging activity with the IC_{50} values of 5.3 and 3.2 µg/ml, respectively (Kalegari *et al*., 2012).

Phosphomolybdenum complex method

Hexane, chloroform, and ethyl acetate fractions of ethanolic leaves extract of *R. induta* showed more than 100% activity in relation to rutin and vitamin C. Hyperin **6** also demonstrated antioxidant activity more than 127.8 % in relation to rutin but only more than 42.3% in relation to vitamin C (Kalegari *et al*., 2012).

CONCLUSION

Rourea sp. is widely used in traditional medicine for various health complaints. Scientific investigation on the plants yielded secondary metabolites of different classes. Several plants of *Rourea* sp. showed potential bioactivity, especially hypoglycemic and antinociceptive activities.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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