PHARMACIA

Pharmacia 70(3): 673–680
DOI 10.3897/pharmacia.70.e106092

Review Article

An updated review of *Typhonium flagelliforme*: phytochemical compound, pharmacological activities and the use of vitexin and isovitexin as flavonoid compound in cosmetics development

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Received 11 May 2023 ♦ **Accepted** 6 August 2023 ♦ **Published** 21 August 2023

Citation: Maha HL, Fidrianny I, Satrialdi, Suciati T (2023) An updated review of *Typhonium flagelliforme*: phytochemical compound, pharmacological activities and the use of vitexin and isovitexin as flavonoid compound in cosmetics development. Pharmacia 70(3): 673–680. https://doi.org/10.3897/pharmacia.70.e106092

Abstract

Typhonium flagelliforme, a plant known for its medicinal properties, has numerous benefits in the treatment of certain diseases. This comprehensive research provides a detailed review of the phytochemical and pharmacological activities of this plant, with a specific focus on the utilization of its flavonoid compounds, namely vitexin and isovitexin, in the development of cosmetic formulas. The phytochemical compounds include flavonoid, coumaric acid, and other polyphenols compounds. These compounds exhibit a wide range of pharmacological activities, including antioxidant, anti-inflammatory, anti-cancer, reduced immunosuppressive effects by reducing lymphocyte proliferation, antibacterial, improved immune system activities, and cured gastric ulcers. Based on these pharmacological activities, this research summarizes the utilization of flavonoid compounds, vitexin, and isovitexin, in developing cosmetic preparations. Subsequently, isovitexin has been shown to possess anti-oxidant and anti-inflammatory, and it shares similar pharmacological effects with vitexin, likely due to its similar chemical structure. Considering the excellent antioxidant capacity of isovitexin, there is a favorable opportunity to utilize it in the creation of cosmetic formulations. Therefore, further research is needed to formulate topical preparations and cosmetics containing *Typhonium flagelliforme* extract.

Keywords

Anti-inflammatory, Antimicrobial, Antioxidant, Herbal cosmetic, Isovitexin, Vitexin, *Typhonium flagelliforme*

Introduction

Typhonium flagelliforme (Lodd.) Blume (TFB) is a medicinal plant from the *Araceae* family, primarily found in Indonesia, Malaysia, and South Korea. Within Indonesia, TFB is distributed across various regions, including Java Island, Kalimantan, Sumatra, and Papua (Widowati and Mudahar 2009). Furthermore, it is commonly referred to as rodent tuber in English or keladi-tikus (Indonesia); it is native to Indonesia. TFB has a long history of use as traditional medicine (Essai 1986), and it is widely recognized for its therapeutic properties in alternative cancer

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therapy, including leukemia, among diverse ethnic communities (Neoh 1992). The tuber of TFB has been utilized as a health care supplement to address various types of cancer, such as breast, lung, rectal, liver, prostate, pancreatic, and cervical cancer, as well as leukemia (Mohan et al. 2008). These plants grow wild in a humid environment that is not exposed to direct sunlight. The entire plant, including the roots (tubers), stems, leaves, and flowers, is used for medicinal purposes (Syahid 2008). According to Nobakht et al. (2010), mature TFB plants could grow up to 26 cm tall. They produce a single inflorescence consisting of a spadix surrounded by a long, slender greenish-yellow spathe. The spathe measures approximately 15.37 ± 1.17 cm in length and 1.44 ± 0.07 cm in width at its widest point. The spadix is divided into four sections: a lower pistillate portion measuring 0.41 ± 0.03 cm, an intermediate portion with sterile flowers measuring 1.48 ± 0.14 cm, a staminate portion measuring 0.34 ± 0.05 cm, and finally, a lemon-yellow rodent tail-like appendix measuring 12.92 ± 1.25 cm. In terms of taxonomy, this plant belongs to the division: Magnoliophyta, class: Liliopsida, subclass: Arecidae, order: Arales, tribe: Araceae, genus: Typhonium, species: *Typhonium flagelliforme* (Lodd.) Blume) (Cronquist 1981). It is a taro-type plant reaching a height of 25 cm to 30 cm, including shrubs, and it thrives in moist environments sheltered from direct sunlight. The leaves are round with a pointed heart-shaped tip, exhibiting a fresh green color. The flat round tuber is as big as a nutmeg (Harfia 2006).

This article was written by collecting and reviewing scientific articles that contain the phytochemical compounds and pharmacological activities of the TFB, and some plants that have been shown to contain vitexin and isovitexin developed in cosmetics preparations. Those articles had been published in the last 15 years, including a minimum of 25 articles in the last 3 years. The articles were presented in PubMed, Google Scholar, Science Direct, Elsevier, and PubChem by using keywords "*Typhonium flagelliforme*", "rodent tuber", "vitexin", "isovitexin". This review article thoroughly discusses TFB as a medicinal raw material, its phytochemical compounds, and basic information on raw material research. In addition, the reviewed articles provide insights into the biologically active substances, their pharmacological properties, the impact of harvesting conditions on the phytochemical profile of TFB, and the potential utilisation these substances in the development of topical formulas.

Phytochemical compounds of *Typhonium flagelliforme*

The phytochemical compounds found in this plant are alkaloids, saponins, steroids, triterpenoids, lignans (polyphenols), glycosides, hexadecanoic acid, and oleic acid (Syahid 2007; Iswantini et al. 2006). TFB produces several chemical constituents, including phenyltridecanoic acid, methyl 13-phenyltridecanoatem, saturated hydrocarbons, aliphatic acids (Choo et al. 2001a), and aromatic fatty acids (Chen et al. 1997). Additionally, through GC-MS analysis, hexadecanoic acid, 1-hexadecene, and phytol derivatives were detected in the dichloromethane extract, and the presence of unsaturated fatty acids in this fraction was confirmed using magnetic resonance spectroscopy (Lai et al. 2008).

In their research, Lai et al. (2010) introduced other compound consisting of oleic acid, linoleic acid, linolenic acid, campesterol, stigmasterol, and β-sitosterol. These compounds are potentially effective as antioxidants, antibacterial, anti-inflammatory, and anticancer. Various extracts from roots, tubers, stems, and leaves were subjected to cytotoxic activity on murine P388 leukemia using an MTT assay. Further analysis of the juice extract contained high levels of arginine (0.874%) determined by the amino acid analyzer. The high tryptophan content (0.800%) was confirmed by NMR and HPLC analysis (Choo et al. 2001a). Furthermore, several common aliphatic compounds such as dodecane, tridecane, tetradecane, pentadecane, hexadecane, heptadecane, octadecane, nonadecane, and eicosane were identified. In a separate investigation, a unique compound called 13-phenyltridecanoic acid methyl ester was isolated and identified using spectroscopic methods (Choo et al. 2001b). Previous research demonstrated that the TFB could produce some secondary metabolites, as shown in Table 1.

Fig. 1, shows the chemical structure of 6 compounds that have been reported in the *Typhonium flagelliforme* leaves, but there are no reports that these compounds are major compounds.

Table 1. Phytochemical compounds in *Typhonium flagelliforme*.

Plant part	Compounds	References
Leaves	Flavonoid (isovitexin)	(Setiawati et al. 2016)
	Flavones; apigenin C-hexoside-C-pentoside, vitexin (apigenin 8-C-glucoside)	(Septaningsih et al. 2021)
	Flavonols; kaempferol 3-O-rutinoside, kaempferol and kaempferol 3-O-(6"-acetyl-galactoside)-7-O-rhamnoside.	
	Hydroxybenzaldehyde; 4-hydroxybenzaldehyde, p-anisaldehyde, p-coumaric acid, quinic acid, cinnamic acid, ferulic acid, p-coumaric α-glucoside acid, caffeic acid, caffeic O-glucoside acid, and vanillin	
Roots	1-O-beta-glucopyranosyl-2- [(2- hydroxyloctadecanoyl) amido] – 4, 8 – octadecadienoic – 1,3- diol, coniferin, β-sitosterol and β-daucosterol, phenylpropanoid glycosides, sterols	(Huang et al. 2004a, b).
Tuber	Methyl esters of hexadecanoic acid, octadecanoic acid, 9-octadecenoic acid and 9,12 octadecadienoic acid	(Choo et al. 2001b)
Whole plant	Pheophorbide-a, pheophorbide-a', pyropheophorbide-a, and methyl pyropheophorbide-a	(Lai et al. 2010)
Oil	Hexadecanoic acid, oleic acid, linoleic acid, linolenic acid, campesterol, stigmasterol and β-sitosterol.	(Lai et al. 2008)

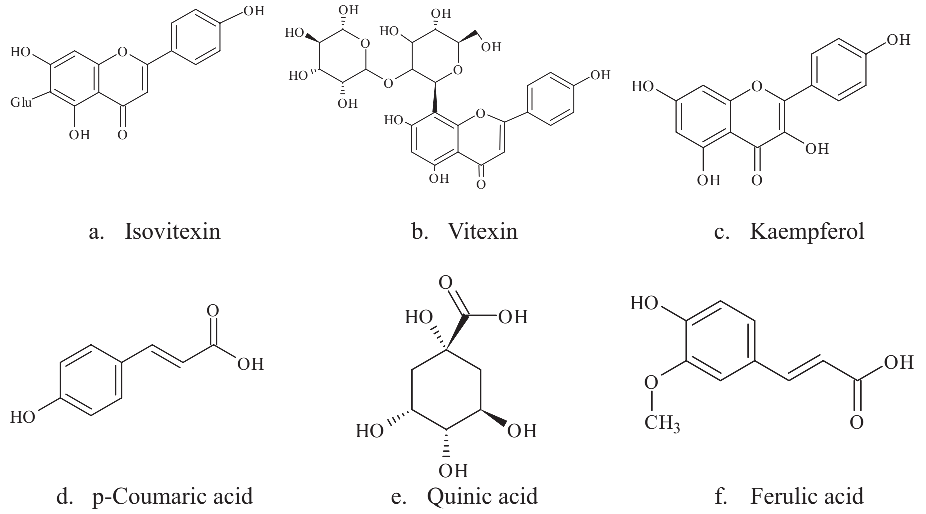

Figure 1. Structure of some chemical compounds from *Typhonium flagelliforme*.

Pharmacological activities of *Typhonium flagelliforme*

TFB, a plant known for its medicinal properties, contains a range of anticancer compounds that are found in various parts of the plant such as the roots, tubers, stems, and leaves (Choo et al. 2001b). Extensive research has demonstrated the effectiveness of the plant in combating several types of cancer, including lung and breast cancer (Lai et al. 2010), liver cancer (Lai et al. 2008), leukemia (Mohan et al. 2010), as well as cancers affecting the intestine, prostate gland, and cervix (Hoesen 2007). Moreover, TFB has shown promising results in preventing breast and uterine cancer (Syahid and Kristina 2007). Other biological activities possessed by the TFB plant included antibacterial and antioxidant effects (Mohan et al. 2008), toxicity to *Artemia salina* (Sianipar et al. 2013), and induced apoptosis (Lai et al. 2008).

Antioxidant activity

Regarding its antioxidant activity, TFB has been found to possess antioxidant potential due to its high content of total phenolic compounds. Ethyl acetate and dichloromethane extracts of TFB at a concentration of 100 μg/mL showed antioxidant potential of 77.6 ± 0.9% and 70.5 ± 1.7% using the DPPH (2,2 diphenyl-1-picrylhydrazyl) method, respectively. These values were comparable to the positive control, BHT, which exhibited 95.3 ± 1.3% inhibition. The total phenolic content was also evaluated, and the dichloromethane extract demonstrated the highest content (5.21 ± 0.82 GAE mg/g extract), followed by the n-hexane extract (3.27 ± 0.85 GAE mg/g) and ethyl acetate extract (2.49 ± 0.33 GAE mg/g) (Mohan et al. 2008). The ethyl acetate fraction of TFB showed that the ethyl acetate fraction gave high activities in exhibiting radical free scavenging DPPH with an IC_{50} value of 56.32 ± 3.13 μg/mL (Farida et al. 2014). Considering the above results, TFB seems to be a good plant with antibacterial and antioxidant activity that requires further investigation. Another investigation by Septaningsih et al. (2021) showed the free radical scavenging activity of ethanol extract of TFB at a concentration of 250 μg/mL with an inhibition value was 35.06±3.05% using the DPPH method, this result could be attributed to kaempferol (flavonoids) content that has been reported in the plant, which has scientifically been proven to be an antioxidant activity (Yoncheva et al. 2020).

Antibacterial activity

In terms of antibacterial activity, TFB has been examined for its antimicrobial properties, particularly in its tubers and leaves. Mohan et al. (2008) reported that the n-hexane extract of TFB tuber exhibited activity against both the Gram-negative bacteria, *Pseudomonas aeruginosa* (11 ± 1.0 mm) and *Salmonella choleraesuis* (12 ± 1.1 mm). TFB n-hexane extract contained saturated fatty acids (Njoku et al. 1997). Saturated fatty acids have been investigated extensively on their antibacterial activity (Kumar et al. 2020; Casillas et al. 2021). Moreover, three extracts (ethyl acetate, n-butanol, and water) of TFB leaves displayed antimicrobial activities in the disc diffusion assay. These extracts inhibited the growth of two bacteria tested (*Pseudomonas aeruginosa* and *Bacillus subtilis*); the highest zone of inhibition against *P. aeruginosa* and *B. subtilis* was seen in ethyl acetate fraction with a concentration of 50% with an inhibition zone diameter of 14.2 ± 0.25 mm and 18.1 ± 0.07 mm respectively (Farida et al. 2014), which was also due to the flavonoid content of this extract. Subsequently, flavonoids were investigated extensively for their antibacterial activity (Biharee et al. 2020; Song et al. 2021), like rutin, quercetin-3-O-glucoside, kaempferol-3-O-glucoside, apigenin-7-O-glucoside, luteolin-7-O-glucoside (Mincheva et al. 2019; Angelina et al. 2021), which are the compounds contained in TFB.

Anti-inflammatory activity

The albumin assay method was used to examine the anti-inflammatory capacity of the ethanol extract of TFB leaves and stems. The results showed that ethanol extract from TFB leaves and stems could significantly inhibit albumin denaturation and membrane stabilization to about 90% and 82%, respectively. The presence of terpenoids might be responsible for the anti-inflammatory effect of the extract (Attah et al. 2022). Furthermore, the ethanol extract showed good anti-inflammatory activity and was comparable to ibuprofen, a standard drug for curing inflammation (Mirgane et al. 2021). Moreover, analgesia and anti-inflammation were examined by the twisting test induced by acetic acid and ear swelling induced by xylene. The water, alcohol, and ester extracts of TFB showed analgesic and anti-inflammatory effects in the twisting test induced by acetic acid and ear swelling induced by xylene. These extracts effectively reduced twisting times and inhibited ear swelling (Zhong et al. 2001). The observed results of the anti-inflammatory activities of the ethanol extract could be attributed to fatty acids, which exhibit anti-inflammatory action (Savych et al. 2020).

Immunosuppressive activity

Regarding its immunosuppressive activity, research has shown that administering the ethanolic extract of TFB at doses ranging from 250 to 1000 mg/kg body weight reduced the immunosuppressive effects on lymphocyte proliferation in cyclophosphamide-treated rats. Moreover, the ethanolic extract of TFB also significantly ($p < 0.05$) improved the immune system activities, specifically the proliferation of CD8+T cells, and reduced the suppressive effects on cytokines such as tumor necrosis factor-α and interleukin-1α (Nurrochmad et al. 2015).

Anti ulcerogenic activity

The extract of TFB exhibited significant suppression in the formation of ulcers, and it was interesting to note the flattening of gastric mucosal folds in rats pretreated with extract (500 mg/kg). Notably, the highest protection of gastric mucosa was observed in rats pre-treated with a 500 mg/kg extract of TFB. Furthermore, the administration of TFB extract prior to ethanol-induced mucosal damage resulted in a significant reduction in both the size and severity of the damage. The inhibitory percentage of effect on gastric ulcers in rats pretreated with a 250 mg/kg extract of TFB was comparable to the effects of omeprazole as a standard drug used for treating gastric ulcers was 87.38% and 86.65%, respectively (Bardi et al. 2011).

Anticancer activity

Regarding its anticancer activity, Crystalia and Hillary (2022) compiled a review that encompassed an investigation conducted on TFB. Five different databases were utilized to conduct a thorough search using specific keywords. The evaluation of TFB's anticancer properties was performed in 30 research involving various types of cancer such as leukemia, lymphoma, breast, oral, cervical, lung, liver, colon, and squamous cell carcinoma. Previous research reported that TFB could inhibit cancer cell proliferation, with most IC_{50} being less than 200 µg/mL (Purwaningsih et al. 2016; Chodidjah et al. 2013). TFB induced an increase in caspase-3 and -9 and a decrease in the anti-apoptotic Bcl-2 protein expression (Chodidjah et al. 2014). In addition, the expression of the p21 protein was increased after the treatment of TFB extract (Putra et al. 2011). In contrast, the tyrosine kinase, Ki67, HER2/neu, telomerase, and COX-2 expressions were decreased, implying that TFB could inhibit tumor growth and development (Chodidjah et al. 2013). Lastly, TFB could also reduce the possibility of cancer cell invasion (Kai et al. 2020). In many investigations carried out, phenolic, terpenoids and alkaloids group compounds are known to have activities that can inhibit growth and kill cancer cells (Juwitaningsih et al. 2022; Mahmod and Talib 2021).

Utilisation of vitexin and isovitexin as flavonoid compounds in cosmetic development

This research showed that TFB contained secondary metabolite compounds such as flavonoids, which have been extensively examined to establish that flavonoid compounds have antioxidant, antibacterial, anti-inflammatory, and anti-cancer activities. Previous research reported that flavonoids from ethyl acetate fraction of methanol extract of TFB leaves were isolated and identified as 6-C-glucosyl apigenin, namely isovitexin (Farida et al. 2012). Isovitexin (apigenin-6-C-glucoside), (Fig. 1a), an isomer of vitexin, containing a 6-C-glycoside compared to 8-C-glucoside in vitexin (He et al. 2016). Isovitexin has also been proven to have various activities, such as anti-oxidant (Mag et al. 2011) and anti-inflammatory (Lin et al. 2005; Lv et al. 2016). Considering the excellent antioxidant capacity of isovitexin, it becomes an opportunity to develop it into cosmetic preparations.

The growing demand for environmentally friendly practices has sparked a surge in the availability of natural cosmetic products in the market. With increasing consumer awareness and recognition of the vast potential offered by natural ingredients, their utilization has expanded across various industries, including pharmaceuticals, nutraceuticals, and cosmeceuticals. In particular, certain herbs have gained popularity due to their antioxidant-rich compositions and their ability to provide protective effects on the skin. TFB is a popular medicinal herb in Indonesia and is well-known for its beneficial antioxidant effects (Mohan et al. 2008; Farida et al. 2014; Septaningsih et al. 2021). Currently, references and investigations on developing cosmetic formulas containing TFB extract are still lacking. Therefore, this research aims to summarize the development of topical formulas from plant extracts containing vitexin or isovitexin.

Table 2. The list of plants containing vitexin and isovitexin, which were used for skin care.

Plant name	Chemical constituent	Dosage form	Beneficial effects on the skin	Results	References
Cecropia pachystachya	Quinic acid, chlorogenic acid isomers, proanthocyanidin dimers type B and C, catechin/ epicatechin, orientin /isoorientin, isoorientin 2”-*O*-xyloside, **vitexin/isovitexin**, and rutin (UHPLC-MS)	Glycolic extracts*	Tyrosinase inhibition for depigmenting activity	Inhibit tyrosinase with IC_{50} = 55.19 ± 4.44 µg/mL, IC_{50} = 19.90 ± 4.41 µg/mL (kojic acid)	(Henrique et al. 2020)
Passiflora coccinea (Aubl.)	C-glycosyl-flavones (ESI-MS/MS) and **isovitexin** (HPLC-DAD)	Methanolic and the glycolic extracts/ emulsion formulation	Sun protector factor activity	The UV spectra showed that both the methanolic and the glycolic *P. coccinea* extracts could absorb the UVB region (320–280 nm). However, the moisturizing topical emulsion formulations containing either the methanolic or the glycolic extracts showed no natural sunscreen properties	(Correa et al. 2020)
Grammatophyllum speciosum	**Vitexin**, Orientin, 3-[(1E)-1-propen-1-yl] pyridine, phenylacetylene, 5,7-dihydroxy-2-(3-hydroxy-4 methoxyphenyl) -4-oxo-4Hchromen- 3-yl-6-deoxy-α-L-mannopyranoside, choline, arginine, histidinediium, phenylacetylene, trigonelline (LC-MS/MS)	Water extracts (leaves)*	Anti-aging functions	Extracts (100 µg/mL) had a capacity for the collagenase-inhibitory effect (25.41% ± 2.18%) compared to the control (p-value ≤ 0.01). The IC_{50} values for DPPH and ABTS were 56 and 117 µg/mL, respectively.	(Yingchutrakul et al. 2021)
Hymenaea martiana Hayne	Astilbin, taxifolin, isoquercitrin, Quercetin-3-O-α-rhamnopyranoside, quercetin-7- O-rhamnoside, kaempferol-7-O-α- *L*-rhamnoside, quercetin, quercitrin, ononin, glycerin, glycerin-6”-O-acetyl, sissotrin, amentoflavone, baicalin, **isovitexin**, apigenin-C-hexosyl, nobiletin, isoxanthoflavan-3-ol (HPLC-ESI-IT)	The crude extract (barks)/Gel preparation	Photoprotective activity	The results showed a synergistic effect between the crude extract and benzophenone-3, bringing promising results for the development of a formulation with photoprotective action with a value of 27.11 ± 0.03	(da Silva Oliveira et al. 2021)
Passiflora nitida Kunth	**Vitexin**, kaempferol-3-O-galactosyl-rhamnosyl-glucoside, gallic acid, ferulic acid, chlorogenic acid, p-coumaric, caffeic and protocatechuic acids, quercetin, kaempferol (LC-MS/MS)	Dry extracts (leaves)*	Depigmentation activity	Decrease in melanin content by 27.1% (B16F10 cells)	(Ribeiro et al. 2022)
Ficus deltoidea	Vitexin (HPLC)	Water extract/ Nanostructured lipid carrier (NLC)	Anti melanogenic activity	Dose of extracts in NLC to 2.7 × 10^{-3}µg/ cm^2 decreased the concentration of melanin to 0.333 µg/mL, signifying a 64.88% of melanin reduction	(Maria et al. 2020)
Viola odorata L.	**Vitexin**, rutin, isovitexin and kaempferol-6-glucoside (HPLC)	Dichloromethane, ethyl acetate, ethanol, and aqueous extracts*	Skin-whitening cosmetics	Inhibited tyrosinase (80.23 ± 0.87% at 100 µg/mL), scavenge NO radical (31.98 ± 0.53 -56.68 ± 1.10%)	(Orhan et al. 2015)
Lannea macrocarpa	4'-methoxy myricetin 3-O-α-L-rhamnopyranoside, myricetin 3-O-α-L-rhamnopyranoside, and myricetin 3-O-α-L-glucopyranoside, **vitexin, isovitexin**, gallic acid and epi-catechin (HPLC)	n-BuOH fraction (leaves)*	Anti-inflammatory topical preparation	In-vivo assay (the croton oil ear test in mice) showed that the extract had a significant anti-inflammatory effect (ID_{50} = 900 µg/cm^2) but ten times lower than standard (indomethacin) with value ID_{50} = 93 µg/ cm^2	(Picerno et al. 2006)
Camellia sinensis	Isoschaftoside, **vitexin**, myricetin 3-O-hexoside, vitexin rhamnoside isomer, quercetin 3-O-glycosides-a, **isovitexin**, rutin, quercetin-O-hexoside, kaempferol-triglyceride-a, kaempferol 3-O-rhamnosyl- (1–6)-glucoside (LC-MS)	Camellia sinensis extracts**	Protective treatment for hair protection	The treatment containing 1000 µg/g tea extract, BIC 29458, showed better protection from photo yellowing than untreated hair and chassis-only (no tea extract) treated hair as measured by both yellowness index.	(Davis et al. 2021)

* No information about dosage form in the research. ** No information on plant parts used for extraction in the research.

Antioxidant and anti-aging activities of flavonoids (vitexin and isovitexin) from plant extracts for cosmetic application

Flavonoids are widely recognized as prevalent and highly sought-after bioactive compounds utilized in the cosmetics industry. Extensive research has been conducted to explore the applications and biological activities of flavonoids in various medicinal plants, i.e., *Eutrema japonicum* (Szewczyk et al. 2021), *Achillea biebersteinii* (Beben et al. 2020), *Cecropia pachystachya* (Henrique et al. 2020), *Alpinia galanga* (Tungmunnithum et al. 2020), *Silybum marianum* (Drouet et al. 2019), *Typhonium flagelliforme* (Sholikha and Puspitasari 2023), etc. Given the multifaceted pharmacological activities often exhibited by flavonoids (Panche et al. 2016), vitexin has emerged as a compound of significant interest in recent times. It has garnered attention due to its diverse range of pharmacological effects, notably encompassing antioxidant properties (An et al. 2012; Babaei et al. 2020) and anti-inflammatory activity (Borghi et al. 2013; Iara et al. 2016), as well as antimicrobial activities (Adamczak 2020; Das et al. 2018). According to current knowledge, isovitexin exerts similar pharmacological effects to vitexin (Fig. 1), partly due to its chemical structure. As shown in Fig. 1, vitexin and isovitexin both have seven hydroxyls, which may contribute to their bioactivities, specifically the O-di-hydroxyl structure in the A ring that was proven to contribute to the effective radical scavenger in flavonoids (Gao et al. 1999) and the stable radical order of hydroxyl in vitexin was found to be 4’-OH>7-OH>5-OH (Praveena et al. 2013).

Plant materials, including extracts, can be applied topically for skin care and the treatment of various skin diseases (Hornfeldt 2005). In addition to the aromatic effects of plants, emphasis is also placed on their antioxidant properties and ability to modulate certain types of skin damage resulting from harmful environmental factors, including ultraviolet radiation (UVR) and free radicals (Chiu and Kimball 2003). This section on potential biological activity aims to provide a comprehensive research overview of the utilization of vitexin and isovitexin in the development of cosmetic formulations derived from diverse plant extracts.

Conclusion

In conclusion, TFB had various phytochemical compounds and pharmacological activities. The phytochemical compounds found in this plant demonstrate antioxidant, anti-inflammatory, and antimicrobial properties. Among these compounds, vitexin and isovitexin, which are flavonoids, play a crucial role and have the potential for utilization in the development of cosmetic preparations. However, further research is required to explore the properties of the compound and formulate topical preparations and cosmetics containing TFB extracts.

Acknowledgments

The authors would like to acknowledge Department of Pharmaceutics and Pharmaceutical Biology, School of Pharmacy, Bandung Institute of Technology, Indonesia, for unlimited support and extended facilities.

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