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Potential anti-inflammation of *Physalis angulata* L.

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Abstract
Physalis angulata is a medicinal plant known for its anti-inflammatory potential. It is used traditionally in the therapy of various inflammation-related diseases. This review aimed to compile information on the anti-inflammatory bioactive compounds from *Physalis angulata*, and their anti-inflammatory mechanisms. Relevant literatures were searched from PubMed and Science Direct. Potential anti-inflammatory bioactive compounds of *Physalis angulata* are phytosterols and non-steroid compounds. The unique phytosterol compounds are Physalins and Withanolides. The non-steroid bioactive compounds are Quercetin, Ursolic acid, Lupeol and Emodin. The anti-inflammation mechanisms are inhibition of macrophage activation, nuclear factor-kappa beta (NF-κB), myeloperoxidase, cyclooxygenase, inducible nitrite oxide synthase, proinflammatory cytokines, monocytes chemoattractant protein-1, and anti-inflammatory cytokines. For therapeutic purposes, extracts of *Physalis angulata* can be administrated as single or adjuvant agent of inflammation-related diseases in several organ systems. Aqueous extract can be consumed orally as herbal drink. Ethanolic or methanolic extracts are available as capsule or cream formula. Various parts of *Physalis angulata* are source of herbal medicine in the treatment of inflammation-related diseases.

Keywords: cecendet, ciplukan, flavonoid, ground cherry, herbal medicine, phytosterol

1. Introduction
Physalis angulata (PA) (Solanaceae, ground cherry, local name: ciplukan, cecendet) is well known traditional medicine in various tropical countries (Fig. 1). PA has several health benefits to treat inflammation-related disorders. Inflammation normally plays a beneficial role in tissue injury against infection, and stimulates tissue healing. But prolonged inflammation is associated with between several health problems. [1] Herbal medicine can be an alternative to overcome this problem. Particular phytosteroid and polyphenolic compounds from herbal materials have anti-inflammatory properties. Besides, their good anti-oxidant activity that abates tissue injury, they have excellent potential to inhibit prolonged inflammation and its progression. [2] Traditionally, water extract or infused water of PA is prepared for herbal drink. Water extraction of PA done by using decoction method [3, 4]. Some dweller in Java boils the whole plants for about 30-45 minutes, while some brew the dried plant in a cup and consumed a day thrice. Nowadays, the researcher develops a new way to administer the extract more pleasantly by turning it into capsules and consumed twice a day. Preparation of the PA extract can be also carried out by Ethanol, Methanol, or using supercritical CO_2. [5-7] PA extracts or raw dry powders are available in the market, as capsule, water extract, cream, herbal tea, and inhaler (Fig. 2). To minimalize inflammation process (pain), some dweller in Indonesia uses pounded PA leaves as wound treatment [8]. This mini review aimed to evaluate the potential anti-inflammation of PA. This review focusses on the bioactive compounds and the mechanisms that associated with the anti-inflammatory capacity. This review discusses 70 citations with their promising anti-inflammatory potential

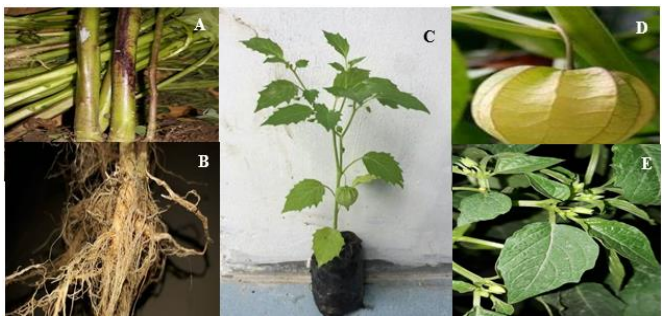

Fig 1: Stem (A), root (B), whole (C), fruit and calyx (D) and leave (E)

Fig 2: Various commercial preparations of *Physalis angulata*

2. Anti-inflammatory bioactive compounds from *Physalis angulata*

Various parts of PA contain phytosteroid and non-steroid compounds that may belong to the potential anti-inflammatory constituents (Table 1.) [9]. The main phytosteroid compounds are Physalins and Withanolides that found in all parts of PA. The non-steroid compounds are Quercetin, Ursolic acids, Emodin, and Luteol that found mainly in leave of PA. Both, phytosteroids and the nonsteroids are commonly found mainly in ethanolic or methanolic extracts (Table 1, 2 and 3). The fruit and calyx are the most enriched part for phytosteroids followed by the stem. The leave is the least in phytosteroid content.

Table 1: List of major phytosterols from *Physalis angulate*

Steroid	Part	Extract	Conc. (mg/g)	Ref.
Physalin B	Leave	EtOH	16.6 ± 4.6	[10]
	Stem	EtOH	45.2 ± 3.1	[10]
Physalin D	Leave	EtOH	11.0 ± 1.4	[10]
	stem	EtOH	42.6 ± 3.3	[10]
	Fruit (Immature)*	MeOH	99.2 ± 8	[11]
	Fruit (Mature)*		25.9 ± 2	[11]
	Calyx* (Immature)	MeOH	788 ± 61,2	[11]
	Calyx * (Mature)		202.8 ± 16	[11]
Physalin F	Leave	EtOH	13.2 ± 3.4	[10]
	Stem	EtOH	43.2 ± 3.0	[10]
Withaferin A	Leave	MeOH	15.54 ± 0.26	[12]
	Stem	MeOH	18.21± 0.39	[12]
	Root	MeOH	18.63 ± 0.34	[12]
Withanolide A**	Leave	MeOH	11.03 ± 0.08	[12]
	root	MeOH	11.33 ± 0.05	[12]
Withanolide B**	Leave	MeOH	7.22 ± 0.13	[12]
Physalucoside A	Whole plant	MeOH	nd	[13]
Physagulin A	Stem & leave	EtOH	nd	[14]
Physagulin C	Stem & leave	EtOH	nd	[14]
Physagulin H	Stem & leave	EtOH	nd	[14]
Campesterol**	Leave	MeOH	10.02 ± 0.31	[12]
b-sitosterol**	Leave	MeOH	16.60 ± 0.26	[12]
b-Sitosterol**	root	MeOH	12.26 ± 0.52	[12]
α-Tocopherol	Whole plant	-	nd	[15]

Note: * from *P. alkekengi*; ** associated with inflammation process; nd: not determined

Phytosteroid compounds: Physalins and Withanolides

Physalins present in the ethanolic or methanolic extracts from calyx, leave, stem and fruit of PA (Fig. 3) [16] Concentrated ethanolic or methanolic extracts from PA are rich in Physalins B, D, and F. [17-19] and Withanolides such as Withaferine A, Withanolide A and B. Additionally, β-Sitosterol, α-Tocopherol and Campesterol are also detectable in PA (Table 2). [12, 17, 18, 20] Particularly, Calyx and fruit of PA are potential source for Physalins and Withanolides. All of them can good extracted with ethanol or methanol. Recently, PA leave is reported as a good Physalin pool. The crude ethanolic extract of the PA leave is rich with Physalins B, D, F, and G. **[21]**

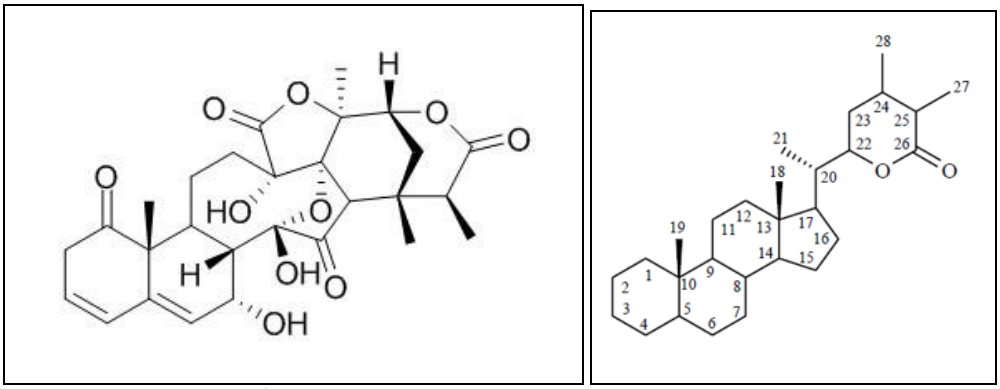

Fig 3: Basic chemical structure of Physalin (A) and Withalonide (B)

2.2 Nonsteroidal anti-inflammatory bioactive compounds

Nonsteroid compounds are often anti-inflammatory bioactive compound. Member of natural phenolic and flavonoid compounds are often found to have anti-inflammatory activity *in vitro* and *in vivo*. Four well known flavonoids found in PA are Quercetin, Ursolic acid, Emodin and Lupeol. Leave extract is good source for Quercetin and Emodin, fruit extract for Lupeol. and stem extract for Ursolic acid (Table 2). All of them can easily extracted with ethanol or methanol. Phenylpropanoids, Chlorogenic acid and Neochlorogenic acid, [10, 12, 16] and phenolic glycosides in PA, such as Physangulosides A and B [22] are detectable also in PA.

Table 2: List of non-steroid bioactive compounds from *Physalis angulate*

Compound	Part	Extract	Group	Conc. (mg/g)	Ref
Quercetin*	Leave	MeOH	Flavonoid	14.28 ± 0.024	[12]
		DCM		2.40	[23]
	Stem	MeOH		3.67 ± 0.03	[12]
Quercetin 3-O-methyl ether	Leave		Flavonoid	2.08	[23]
Isoquercetin*	Leave		Flavonoid	1.60	[23]
Myricetin 3-O-neohesperidoside	Whole	EtOH	Flavonoid	0.034	[24]
Lupeol*	Leave	MeOH	Triterpene	5.42 ± 0.44	[12]
	Stem			0.44 ± 0.18	[12]
	Fruit			23.93 ± 0.16	[12]
	Root			1.66 ± 0.37	[12]
Ursolic Acid*	Leave	MeOH	Triterpenes	3.52 ± 0.38	[12]
	Stem			13.19 ± 0.24	[12]
	Fruit			3.98 ± 0.44	[12]
	Root			2.81 ± 0.28	[12]
Emodin*	Leave	MeOH	Anthraquinone	5.92 ± 0.39	[12]
	Stem			0.39 ± 0.34	[12]
	Fruit			0.91 ± 0.78	[12]
	Root			2.67 ± 0.44	[12]
Chlorogenic and Neochlorogenic	Root	MeOH	Phenylpropanoid	NA	[17]
Physangulosides A	Leave	MeOH	Phenolic glycoside	NA	[22]
	Stem			NA	[22]
	Fruit			NA	[22]
	Root			NA	[22]
Physangulosides B	Leave	MeOH	Phenolic glycoside	NA	[22]
	Stem			NA	[22]
	Fruit			NA	[22]
	Root			NA	[22]
Squalen-1-ol	Whole plant	MeOH	Squalene derivate	NA	[15]
Squalene	Whole plant	MeOH	Squalene derivate	NA	[15]
Phytol	Whole plant	MeOH	Squalene derivate	NA	[15]

Note: *associated with inflammation process; NA: no/weak activity; DCM: dichloromethane

3. Anti-inflammatory mechanisms of phytosterol from *Physalis angulata*

The role of herbal material on the immune response can be divided into two groups, namely immunomodulation and anti-inflammation. Immunomodulation is a very important manner to bind immune system with pathogenic bacteria. Recently,

Daltro, S. R. T., *et al*. (2021) reported that ethanolic extract of PA has immunomodulatory activities. [25] By enhancing immunomodulation process, opsonisation and phagocytosis become more intense. PA is one of the herbal materials that can regulate immune system, such as lymphocytes proliferation and Janus Kinase pathway. [26, 27] The increment of immunomodulation can result in increase of anti-inflammation response.

Bioactive component of PA (BCPA) shows interaction with several molecules target associated with the inflammatory process (Fig. 2). BCPA reduces inflammation process through several modes of action. At least, eight mechanisms of inflammation are associated with the bioactive compounds in PA (Table 3).

BCPA inhibits the macrophage activation. BCPA can directly reduce cytokine production by affecting local inflammatory response of the macrophage cells, as well as systemic responses sequentially. [28, 29] Dichloromethane fraction of PA calyces (PADF) has also an anti-inflammatory activity. PADF fraction is able to prevent the induction of cyclooxygenase-2 (COX-2), interleukin (IL)-1β, IL-6, IL-12, and inducible nitric oxide synthase (iNOS), and tumour necrosis factor (TNF-α), but increase the quantities of arginase (ARG1), IL-10, and mannose receptor C (MRC1) [30] that are determined by the anti-inflammatory genes.

3.1 Anti-inflammatory mechanisms of Physalins and Withanolides

Phytosterols, such as Physalins and Withanolides, are active in several anti-inflammatory processes (Table 3), namely

- Stimulation of anti-inflammatory cytokines, such as interleukin 10 (IL-10) and transforming growth factor-beta (TGF-β)
- Inhibition of cyclooxygenase-2 (COX2),
- Inhibition in the production of proinflammatory cytokines,
- Inhibition of monocytes chemoattractant protein 1 (MCP-1) and chemokines CCL7 and CXCL8 activity

Physalin A can take role in Interfering Nuclear factor-kappa beta (NF-κB) signalling pathways. Suppressing Ikβ (inhibitor of NF-κB) protein degradation results in decreased NF-kβ p65 protein [20, 31-34], and suppressed glucocorticoid receptors activation [28, 35, 36] additionally, they also decrease reactive oxygen species (ROS) which play an important role to induce oxidative stress and enhance inflammation. Physalin A can increase the antioxidant factor levels of SOD, CAT, and GPx. By suppressions of the JNK/AP-1 and IκB/NF-κB signalling pathways and up-regulation of the anti-oxidative activity, Physalin A is able to develop its anti-inflammatory potentials. [28]

Anti-inflammatory capacity of Physalin A is determined by its inhibitory activities on

- The expression of inflammatory cytokines (PGE(2), IL-1β, IL-6, NO, and TNF-α);
- The IκB/NF-κB and JNK/AP-1 inflammatory signalling pathways;
- The production of pro-inflammatory factors iNOS and COX-2; and
- The production of inflammatory mediators such as MDA, NO, and TNF-α production.

COX2 is responsible for the prostanoid synthesis. Inhibitors of prostanoid synthesis such as prostaglandin and thromboxane, can improve pain perception, inflammatory responses, and affect platelets aggregation. Physalins (B, D, F, and G) that usually in concentrated ethanol extracts (CEEPA) have an antinociceptive effect. In addition, CEEPA decrease the quantity of TNF-α, IL-1β, COX-2 and iNOS mRNA. [19]

Physalin B from PA has anti-inflammatory activity and effects on macrophages. It inhibit significantly the expression and secretion of tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and NF-κB nuclear translocation. Physalin B can suppress inflammatory response in macrophages by inhibiting the production of inflammatory cytokines via NF-κB signaling. [37]

Physalin E has anti-inflammatory effect on either acute or chronic dermatitis. The changes in ear oedema/thickness, production of pro-inflammatory cytokines (TNF-alpha and IFN-gamma), myeloperoxidase (MPO) activity, and histological and immunohistochemical findings are indicators of dermal inflammation. Physalin E may be a potent topically effective anti-inflammatory agent useful to treat the acute and chronic skin inflammatory conditions. [38]

Physalin E has an anti-inflammatory effect on acute and chronic models of dermatitis. Therefore, it is potential and effective topically anti-inflammatory agent that useful to treat the skin inflammatory conditions. [38] Physalin E play roles in glucocorticoid receptor and reduced the ear oedema response and the MPO activity. Unlike Physalin B, D and F, Physalin E do not have cytotoxicity effect. [39]

3.2 Anti-inflammation mechanism of Withangulatin A

Withangulatin A has anti-inflammatory potential that significantly suppress T lymphocytes proliferation and inhibit pro-inflammation cytokines (IL-2, IL-6 and IFN-gamma). Its ability to reduce the COX-2 expression is mediated by MAPKs and NF-κB nuclear translocation pathways. Interestingly, administration of Withangulatin A inhibits the extent of mice ear swelling and decreases the pro-inflammatory cytokines production in mice blood serum. Withangulatin A influences the T lymphocytes function through targeted inhibiting COX-2 expression via MAPKs and NF-κB nuclear translocation signalling pathways. Moreover, Withangulatin A can significantly suppress T lymphocytes proliferation and inhibit pro-inflammation cytokines (IL-2, IL-6 and IFN-gamma). [40] Therefore, these capacities will make Withangulatin A as a strong candidate for further study as an anti-inflammatory agent. [40]

It is reported that ethanolic extract/fraction of PA calyxes have ability to modulate MCP-1 expression. [41] Monocyte chemoattractant protein-1 (MCP-1) is a potent chemoattractant for monocytes and macrophages to areas of inflammation, and implicated in multiple inflammatory diseases. [42] In normal states of inflammation response, chemokines such as MCP-1 can signal the activation of mast cell, eosinophiles, and macrophages to aggregates the pathogens. It is supposed that the inhibition of MCP-1 activity caused by the action of Withaferin A which inhibits almost every inflammation mediator not specifically on MCP-1. [43, 44]

Table 4: Anti-inflammatory mechanisms of phytosterols from *Physalis angulata*

Mechanism	Physalins	Withanoids
Inhibition of macrophage activation	-	-
Inhibition of chemokines Monocyte chemoattractant protein-1 (MCP-1)	-	Withaferin A
Inhibition of CCL7 and CXCL8 activity	-	Withaferin A
Interfering Nuclear factor-kappa beta (NF-κB) signaling pathways	Physalin A [20, 31-34], B[37],	Withangulatin A[40]
Inhibition of myeloperoxidase	Physalin E[38]	-
Inhibition of cyclooxygenase-2 (COX2)	Physalin A,[36]B, D, F and G [19]	Withangulatin A[40]
Inhibition of inducible nitrite oxide synthase (iNOS)	Physalin A, [36] B, D, F and G[19]	-
Inhibition in the production of proinflammatory cytokines (PGE(2), IL-1β, IL-6, NO, and TNF-α)	Physalin A,[36] B, E [38]	Withangulatin A[40]
Stimulation of anti-inflammatory cytokines, such as interleukin 10 (IL-10) and transforming growth factor-beta (TGF-β)	-	-
Inhibition of Prostaglandin E2 (PGE2)	Physalin A[28]	-
Inhibition of lymphocyte proliferation	-	Withangulatin A [40]
Increasing mRNA expression levels of *Hif-1α*, *Sod-2*, and *Ho-1*	-	-

The anti-inflammatory activity of P. angulata is due primarily to its withanolide content. [13] Withanolides is promising candidates for the development of new anti-inflammatory drugs. Recently, Wang, L., *et al*. (2021) reported that three withanolides, Physagulin A, C and H, can block NF-κB signaling pathway, and therefore have anti-inflammatory activities. Physagulin A, C, and H are not only able to inhibit the release of NO, PGE(2), IL-6 and TNF-α, but also can down-regulate the expression of iNOS and COX-2 proteins. Furthermore, Physagulin A, C, and H can block the degradation of IκB-α and the nuclear translocation of NF-κB/p65. However, none of them could inhibit the phosphorylation of MAPKs family proteins ERK, JNK and p38. Thus, the anti-inflammatory actions of Physagulin A, C, and H are mainly due to the significant inhibition of NF-κB signaling pathway rather than MAPKs signaling pathway. Physagulin A, C, and H exhibit potent anti-inflammatory activity and can be used as NF-κB inhibitors. [14]

Excessive inflammation is a critical factor in many human diseases. PA extracts are source of anti-inflammation agents that can be used in the treatment of inflammation-related diseases (Table 5).

Table 5: treatment of inflammation related diseases with phytosteroids from *Physalis angulate*

inflammation	Extract	Description
Skin inflammation: infection, wound, dermatitis	PACO2 extract	Reduce cytokine production. Improvement in skin microcirculation and lowering skin temperature [8]. Reduce the production of inflammatory mediators and maintaining IL-10 production.
rheumatoid inflammation	Methanolic extract	Reduce aspartate transaminase (AST) and alanine transaminase (ALT) level [45].
Cancer related inflammation	PA extract	Ameliorate inflammation that directly induce apoptosis. [46, 47]
	Withangulatin A	Suppress inflammation by inhibiting COX-2 expression through MAPKs and NF-kappaB signalling pathways. [40]
Inflammatory Bowel Disease	Dichloromethane	Maintain the inflammation process reduces proinflammatory cytokines and neutrophil infiltration. [6, 30] Calyces PADF has an immunomodulatory effect in activated macrophages and prevent the induction of interleukin (IL)-1β, tumour necrosis factor (TNF-α), IL-6, IL-12, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) [30]
Inflammation-Neurological Disease	aqueous extract	Antinociceptive effects and improves pain. Physalin B, D, F, and G significantly ameliorate acetic acid-induced pain. Physalin F can improve sign of inflammation such as hyperalgesia, oedema, and reduce local production of TNF-α which associated with central stimulation.[48]
Inflammation-Autoimmune disease	Ethanolic extract	Immunosuppressive effect [49, 50]
Inflammatory Respiratory Disease	Methanolic extract	ameliorates allergic reaction [7] Physalin F does not show effect in mice with allergic airway inflammation, [45, 51] but other compound (not Physalin F) in PA may associate with allergic inflammation. [7]

4. Anti-inflammatory mechanisms of NSAID from *Physalis angulata*

The Nonsteroidal anti-inflammatory drugs (NSAID), particularly phenolic and flavonoids, are important drugs that reduce the symptoms of inflammation. They have specific their mode of action, that are not similar with the phytosteroids, namely

- Inhibition of monocytes chemoattractant protein 1 (MCP-1) and chemokines CCL7 and CXCL8 activity,
- Stimulation of anti-inflammatory cytokines, such as interleukin 10 (IL-10) and transforming growth factor-beta (TGF-β) [52], and
- Modulation the expression of pro-inflammatory genes (cyclooxygenase, lipoxygenase, nitric oxide synthase, and several essential cytokines), by signalling nuclear factor-kappa B and mitogen-activated protein kinase.[53]

Quercetin is known for its broad range of activities. Quercetin has a biphasic behaviour that can play a regulatory action on immunity and inflammation [54]. The analgesic property of quercetin, intrinsically linked to its anti-inflammatory activity.

[55] Quercetin inhibit ER stress-associated TXNIP and NLRP3 inflammasome activation, and thereby protect endothelial cells from inflammatory and apoptotic damage. [56] Quercetin is able to inhibit NF-kappaB signalling pathway [57] In fact, as pure flavonoid, Quercetin or enriched-extracts, can reduce the expression of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β and COX-2), down-regulate inflammatory markers, and effects on MAPKs [58]. Quercetin is often found in its glycoside such as Isoquercetin, that may have better bioavailability than quercetin with the same therapeutic effects [73, 60].

Ursolic acid has a good anti-inflammatory property [61]. But its water solubility is low water solubility [62, 63]. Ursolic acid and Emodin can inhibit monocytes chemoattractant protein 1 (MCP-1) [64] and chemokines CCL7 and CXCL8 activity [43, 44, 65] Ursolic acid (UA) is a promising molecule with anti-inflammatory, analgesic and potential anti-arthritic activity [66] In silico and docking studies, two triterpenoids, Ursolic acid and Lupeol, show that both possess immunomodulatory and anti-inflammatory activity, due to high binding affinity to human receptors viz., NF-kappaB p52, tumour necrosis factor (TNF-alpha), nuclear factor NF-Kappa-B P50 and cyclooxygenase-2. Both show significant increase in humoral immune function, but no significant changes are observed in cell mediated immune response and haematological parameters. [67]

Emodin inhibit LPS-induced NO production in concentration-dependently. Emodin also inhibit LPS-induced iNOS protein, but it inhibit LPS-induced iNOS mRNA expression only slightly and did not affect COX-2 mRNA and proteins. Furthermore, Emodin do not block nuclear factor-kappaB (NF-kappaB) binding and transcriptional activation associated with decreased p65 proteins in the nucleus induced by LPS. Emodin inhibition of LPS-induced iNOS expression may be mediated by a different transcription factor [68]. Emodin is an anthraquinone that has potential anti-inflammation effect. It is able to suppress mitogen-activated protein kinases (MAPKs) and nuclear factor-κB (NF-κB) activation in lipopolysaccharide (LPS)-activated RAW 264.7 cells [69].

As in the case of Ursolic acid, Lupeol has a good anti-inflammatory property [70] and a low water solubility [62, 63]. Lupeol can stimulate the expressions of cytokines and growth factors that involved in wound healing. The wound healing activity of Lupeol decreases inflammatory cell infiltration, and increases proliferation of fibroblasts, vascularization, and deposition of collagen fibres. Lupeol treatment results

- A decreased intensity of NF-*κ*B and increased intensity of FGF-2, TGF-*β*1, and collagen III;
- A downregulated IL-6 levels and upregulated IL-10 levels;
- An increased mRNA expression levels of *Hif-1α*, *Sod-2*, and *Ho-1* [71].

Table 4: Anti-inflammatory mechanisms bioactive compounds of NSAID from *Physalis angulate*

Mechanism	NSAID
Inhibition of macrophage activation	Quercetin
Inhibition of chemokines Monocyte chemoattractant protein-1 (MCP-1)	Ursolic acid, Emodin [64]
Inhibition of CCL7 and CXCL8 activity	Ursolic acid, Emodin [43, 44, 65]
Interfering Nuclear factor-kappa beta (NF-κB) signaling pathways	Quercetin [57], Ursolic acid[67] Lupeol[67]
Inhibition of myeloperoxidase	-
Inhibition of cyclooxygenase-2 (COX2)	Ursolic acid[67], Lupeol[67],
Inhibition of inducible nitrite oxide synthase (iNOS)	Emodin [68]
Inhibition in the production of proinflammatory cytokines (PGE(2), IL-1β, IL-6, NO, and TNF-α)	Quercetin [57], Ursolic acid[67], Lupeol[67] [71]
Stimulation of anti-inflammatory cytokines, such as interleukin 10 (IL-10) and transforming growth factor-beta (TGF-β)	Lupeol [71]
Inhibition of Prostaglandin E2 (PGE2)	-
Inhibition of lymphocyte proliferation	-
Incresing mRNA expression levels of *Hif-1α*, *Sod-2*, and *Ho-1*	Lupeol [71]

4. Conclusions and recommendations

4.1 Conclusions

Several conclusions or highlights of this review are as follows

- Even traditionally, aqueous extract as PA-herbal drink is the most popular and easiest and safe preparation of PA-delivery, it is less researched than ethanolic or methanolic extracts.
- Two groups of anti-inflammatory bioactive compounds of PA are phytosteroids, mostly Physalin, Withanolides, and non-steroids (Quercetin, Ursolic acid, Emolin, and Lupeol).
- Ethanolic and methanolic extracts are the most frequent method to maximize the ciplukan's extract anti-inflammatory potential.
- Calyx and fruit of PA are best source for Physalins, Withanolides, and the non-steroids. Leave of PA is the best source for the non-steroid compounds, particularly Quercetin and Emodin.
- Crude extracts, purified phytosterol or non-steroid compounds, exhibit differently on various types of inflammation mechanisms.

4.2 Recommendations

- PA raw materials or extracts can be a future anti-inflammation drug potential through more intensive research. However, further researches are needed in developing an innovative therapy with PA products that show their efficacy in various diseases. Several research areas are urgent, namely
- The effective and efficient extractions, conventional and unconventional methods, particularly water extraction of various parts of PA.
- The systemic bioavailability in utilizing PA extract for the treatment of various inflammation-related disease that followed with the right preparation and dose.
- The application of microencapsulation and nanotechnology, particularly for the bioactive compounds which have a low water solubility.

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