Mechanism of Action and Phytochemicals of Some Potential Analgesic Agents from Indian Natural Product: A Review

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ABSTRACT: Analgesics are class of drugs used to treat pain. Pain is sensory and emotional experience which is unpleasant that doesn’t related with the actual or potential tissue damage or circumstances which depicts the damage itself. Generally analgesics side effect is peptic ulcer. Indian society, hereditary and traditionally, used natural products as a treatment. Plants produce secondary metabolites to overcome various diseases. Pharmacological effects on natural products are due to the synergism effect and polyvalent activity. This paper aims to review the potential analgesic agents and action of mechanism of phytochemicals from Indian natural products for the further improvement of its utility in curing pain and maintaining good health. Based on this, the pain can be overcome by using various natural products including Aloe Vera (Aloe vera), Papaya (Carica papaya), Noni (Morinda citrifolia), Ginger (Zingiber officinale), Kalmegh (Andrographis paniculata), Betel (Piper betle), and Turmeric (Curcuma longa). In general, the mechanism of the plants to relieve the pain is by suppressing the expression of cyclo-oxygenase (COX-2).

KEYWORDS: Analgesics, natural products, pain.

I. INTRODUCTION

Pain is one signal of tissue damage due to mechanical, chemical or physical stimulation. Pain perception is supported by neuro-sensory system and afferent nerve lanes, which especially responding to potential harm [1]. Pain which caused by mechanic, chemical, or physic (calor, electricity) stimulus could rise the potential damage to the tissue [2]. It stimulates the release of certain substances called pain mediator such as histamine, bradykinin, leukotrien, and prosta
glandin [1]. Those entire pain mediators stimulate pain receptors which channel the stimulation to the brain through the nerves points which has many synapse through spinal cord, marrow advanced, and midbrain. From thalamus impulse stimulus then transferred to the pain center in the large brain, where the impulse is felt as pain. Analgesics are class of drugs used to treat pain. Generally analgesics side effect is peptic ulcer [2].

Plants-based medication has become the tradition and culture in every ethnic in the world especially in India. Plants contain secondary metabolites which have the important value in pharmacology field and can be used to cure many diseases [3]. Pharmacological effects on natural products due to the synergism effect and polyvalent activity [4]. Based on that, the pain can be cured by herbal medications. Plants produced secondary metabolites to overcome various diseases. This paper aims to review the potential analgesic agents and action mechanism of phytochemical from Indian natural products for the further improvement of its utility in curing pain and maintaining good health.

II. RESULT AND DISCUSSION

a) Aloe Vera (Aloe vera)

Aloe vera contains secondary metabolite such as flavonoids [5], tannin [6,7], saponins, glycoside, alkaloid [8,9] terpenoids, phlobatannin [10,11] and anthraquinone [6]. A group of workers stated that aloe vera extract which has a function as anti-arthritis [12] is anthraquinone while another group stated that aloe vera contain of lupeol and salicylic acid which are the effective compounds as pain reliever [13].

Ethanol and methanol extract from aloe vera are proven to have activities that can relieve the pain. It has been proven through the in vitro study which shows that the extract, could potentially suppress the expression of cyclo-oxygenase (COX-2) [14], as one of the way the NSAID medicine works. It has also been proven through in vivo where ethanol and methanol could significantly increase the analgesic effect when it is injected to rats [15]. The analgesic activity is derived from the existence of carboxypeptidase and bradikinase enzyme which function is to lessen or to relieve the pain. The reduction of pain happens when immune system is stimulated and blocked the biosynthesis prostaglandin [14] which is responsible for the occurrence of pain [10,16].

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 According to another research, 300mg/kg dose of aloe vera infusion is effective as analgesic for somatic pain and for internal body pain without any side effects for kidneys and liver [1].

b) Papaya (Carica papaya)

Papaya leaves contain vitamin E, glycoside, alkaloid, saponin, carposid, sucrose, dextrose, levulosa, papain enzyme, pseudocarpain [17], steroid, quinone, antheraquione, [18], tannin [19] and flavanoid [20]. Papain and chymopapain are the strong component to be the active compounds which produce analgesic effect to the extract of papaya’s leaves [18].

Papaya leaves has been proven to have analgesic activity [21]. It is caused by ethanol extract of papaya leaves contain of flavanoid which has been known could block inflammatory formation that causes the pain. Flavanoid blocks cyclooxygenase I (COX I) which has a role in prostaglandin biosynthesis as pain formation mediator, so that it will blocks the occurrence of pain [19]. Papaya leaves also has papain enzyme which has analgesic activity. Methanol extract of Papaya seeds also had been proven could lessen the pain with possible mechanism which inhabiting pain mediator such as histamine, prostaglandin, and sitokin [21-23].

c) Noni (Morinda citrifolia)

Noni fruits contain 90% water and other crucial substances such as glutamate acid, aspartat acid, isoleusin, fenol substances (scopoletin, proxeronine, xeronine, morindone rubiadiin), antheraquione [24], askorbat acid, pro-vitamin A [25], alkaloid, and terpenoid [26]. There are also other substances in Noni which expected to have analgesic quality such as proxeronine and xeronine.

The extract of Noni shows the significant analgesic effect when it was given to the mice. The administration and 2 of Noni’s juice to mice has increasing mice’s tolerance to the pain. The extract of Noni is expected to block histamine and prostaglandin receptors hich are the receptors of pain. Noni’s ethanol extract has better analgesic effect than paracetamol to the mice [24]. Besides, it has been proven that 75% of aqueous extract of noni’s roots had the same potency as morphine. On that dose it doesn’t causes addiction effect, side effects [26], and toxic effects [24]. A group of scientists proved that the aqueous extract of Noni’s seeds 8 mg/kg dose has shown a significant analgesic effects [27].

d) Ginger (Zingiber officinale)

The content of secondary metabolite on ginger rhizome are alkaloid, flavanoid, saponin, tanin, terpenoid, steroid [28], gingiberin (20,57%), beta seiqufelandrin (12,71%), kurkumin (11,27%), gingerol (4,46%), shogaol, paradol, gingerdione [29,30]. Gingerol and Shargaol are the compounds which responsible for analgesic activity on ginger rhizome [31].

Ginger has been proven could inhibit prostaglandin biosynthesis which has the same mechanism as Non-Steroidal Anti-Inflammatory Drugs (NSAID) [29]. Based on the result of in vitro study, ginger rhizome and its main compounds such as gingerol and shargaol could block COX enzyme synthesis and pain mediator synthesis such as prostaglandin and leukotrin [31,32]. Based on research, it is listed from the one which has the highest effect on its content to block the COX-2 enzyme synthesis is paradol, shogaol, gingerol and gingerdione. Another research work has proved that ginger rhizome has an effect to several genes which encoding sitokin, kemokin and COX-2 enzyme [33].

e) Kalmegh (Andrographis paniculata)

A review of the literature reveals that the presence of various chemical constituents in the aerial parts of the Andrographis paniculata are andrographolide, which is diterpene lactone, colourless, crystalline, bitter in taste [34]. Other compounds include 14-deoxy-11-oxoandrographolide, didehydro andrographolide /andrographolide D, 14-deoxyandrographolide, non-bitter compound is neo andrographolide, homoandrographolide, andrographosterin, andrograpanin, a-sitosterol, stigmasterol. Apigenin-7, 4-dio-methyl ether, 5- hydroxy 7,8,2, 3-trimethoxy flavones, monohydroxy trimethyl flavones, andrographin, dihydroxy dimethoxy flavone, andrographone, andrographoside, andropanali-culoside, andrograpanin, Isoandrographolide and skollicaflavone. Six entfadbane diterpenoids i.e. 3-o-beta-D-glucopyranosyl-14, 19- di-deoxy-andrographolide, 14-deox, 17- hydroxyl andrographolide, 19-o-[beta-D-apiofuranoxy 1-2beta- D-glucopyranoyl]-3, 14-dideoxyandragrapholide, 3-beta-Dglucopyranosyl- andro-grapholide, 12S-hydroxy andrographolide and andragraphatoside. These compounds showed inhibitor activity against several fungal and bacterial strains. Dua et al. reported four xanthones 1,8-di hydroxyl 3,7- dimethoxy xanthone, 4,8-di-hydroxy-2, 7- dimethoxyxanthones, 1,2-dihydoxy-6, 8-di methoxy xanthone and 3,7,8-trimethoxy-1-hydroxyxanthone from the roots [35,36].

Andrographolide is the main active component of these plants [37]. Androghapolide which is being isolated from Bitter leaves is responsible to the analgesic activities of that plant. Andrographolide which is being isolated from extract Kalmegh leaves has been proven to have significant analgesic activity on 300mg/kg dose.

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Its mechanism is by reducing the expression process of COX-2 and reducing the expression gene of COX-1 [38], and also releasing the pain mediator histamine [34].

f) Betel (Piper Betle)

The compounds in Betel leaves are alkaloid, tanin [39], alipirokatekol, kavibetol, eugenol, dan safrol [40]. The active compound which responsible for analgesic activity of betel leaves is eugenol [40]. The methanol extract of betel has been proven to have significant analgesic activities even though the result is not as good as narcotic analgesic [41], the analgesic activity is significantly shown that it could decrease the histamine production [42,43], it is also shown that its mechanism works in the central of pain receptor which is in the center of nerve system [44]. Eugenol’s analgesic activities stated to have mechanisms as gene suppression and its function is to express siklooksigenase-2 enzyme (COX-2) [40].

g) Turmeric (Curcuma longa)

The compounds in turmeric rhizome are curcumin [45], flavanoid, glikoside, phenol [46], alkaloid, saponin, tanin [47], phtlobatanin, antosianin [48]. The active components which responsible for turmeric analgesic activity is curcumin [49,50]. The research done by [51], found that curcumin gave significant analgesic effect when it was examined to the rats. Curcumin reported to work by suppressing siklooksigenase-2 (COX-2) enzyme production which responsible for prostaglandin sinthesis process [52], it even be said that curcumin can relieve the pain with the same mechanism as NSAID [45]. The research done by [53], curcumin has been proven to decrease siklooksigenase-2 (COX-2) level on mice. Curcumin has also been proven can lessen the pain in neuropathic disease by inhibiting CBP Histone acetyltransferase which function to regulate the expression of COX-2 on mice [49]. The research done by [54], showed the significant analgesic activity was proven by Tail-flick method on albino rat. Turmeric leaves has also been proven could lessen the pain caused by chronic pain which occur in rheumatoid arthritis disease or cancer [47].

III. CONCLUSION

Pain can be overcome by using natural products including Aloe Vera (Aloe vera), Papaya (Carica papayya), Noni (Morinda citrifolia), Ginger (Zingiber officinale), Kalmegh (Andrographis paniculata), Betel (Piper betle), and Turmeric (Curcuma longa). The general mechanism of the plants to relieve the pain is by suppressing the expression of cyclo-oxygenase (COX-2).

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