Plants Possessing Potential Analgesic And Anti-Inflammatory Activities: A Review

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Abstract – The side effects resulted due to the therapy of classical Non-steroidal anti-inflammatory drugs (NSAIDs) and the opoids in the management of pain and inflammatory conditions are major problems. Researches have been carried out still inorder to have novel analgesic, anti-inflammatory agents with no side effects. As plants based medicines are found with minimal side effects, they have gained much attention in this regard. This review article is a try to provide an overview of reported analgesic and anti-inflammatory activities of fifteen plants with interesting profile of activities.

Keywords – Analgesic, Anti-inflammatory, Extract, Evaluation

Introduction

The nature has provided a complete source of remedies to cure the diseases of mankind and is best friend of pharmacy. The natural drugs are effective in action without side effects. Drugs obtained from plant source constitute a major part of therapeutics in the traditional systems of medicine. Herbal medicine is a triumph of popular therapeutic diversity.

Plants are valuable for modern medicine as they are used as sources of direct therapeutic agents, serve as raw materials for elaboration of more complex semi synthetic chemical compounds, chemical structures derived from plant sources can be used as models for new synthetic compounds and plants can be used as taxonomic markers for the discovery of new compounds [1].

Pain is a subjective experience which is hard to define exactly. Typically, it is a direct response to an untoward event associated with tissue damage, such as injury, inflammation or cancer, but severe pain can arise independently of any obvious predisposing cause (e.g. trigeminal neuralgia), or persist long after the precipitating injury has healed (e.g. phantom limb pain). The management of pain is always multidisciplinary and involves pharmacotherapy, cognitive behavioral therapy and physiotherapy. Pain can be classified into two types: Integumental pain which is superficial and related to skin muscle and joints and visceral pain which is deep seated and related to heart, kidney, stomach, gall bladder etc. The cause of the pain may be physiologic, inflammation and neuropathic. Analgesics are the drugs which decrease the pain sensation. There are 2 types of analgesic agents: Opioid analgesics and Non steroidal anti-inflammatory agents (NSAIDs). Opiod analgesics are mainly used to treat visceral pain while NSAIDs are most commonly employed agents for the treatment of integumental pain [2].

The inflammatory process is the response to an injurious stimulus. It involves a complex array of enzyme activation, mediator release, extravasations of fluid, cell migration, tissue breakdown and repair [3-4]. No matter what the initiating stimulus, the classic inflammatory response includes calor (warmth), dolor (pain), rubor (redness), and tumor (swelling).Inflammatory responses occur in three distinct temporal phases, each of which apparently mediated by different mechanisms: an acute phase, characterized by transient local vasodilation and increased capillary permeability; a delayed, subacute phase characterized by infiltration of leukocytes and phagocytic cells and a chronic proliferative phase, in which tissue degeneration and fibrosis occur [5]. Steroidal anti-inflammatory drugs and more commonly non-steroidal anti-inflammatory drugs are used in the therapeutics for the treatment of inflammatory conditions. Classical non-steroidal anti-inflammatory drugs (NSAIDs) have nonselective action towards cyclooxygenase (1 and 2) which results in certain mechanism based side effects like dyspepsia, gastrointestinal ulcerations, bleeding and nephrotoxicity [6]. The major drawback of NSAIDs is their gastric ulcer formation due to gastric irritation while opioid therapy is associated with induction of tolerance and dependence, so they are not successful in all cases [7,8].

Therefore development of new analgesic and anti-inflammatory drugs lacking these side effects is still a challenging task and researches are being carried out in order to have alternatives to NSAID and opiates. Plant-based drugs gained a lot of attention in this regard. This review article is a small attempt to cumulate the efforts of various researchers who have evaluated the analgesic and anti-inflammatory activities of various plants. The article includes analgesic and anti-inflammatory activity of twenty five plants. Discussion includes the model used for evaluation of activity, test dosages, standard drug used for comparison, comparative results and discussion made by various researchers.

Plants Possessing Analgesic and Anti-Inflammatory Activities

1. *Melanthera scandens*

Jude E Okokon et.al evaluated the anti-inflammatory and analgesic activities of ethanolic leaf extract of Melanthera scandens. Anti-inflammatory activity was investigated using carrageenan induced hind paw edema and egg albumin induced edema method in mice. Whereas the analgesic

activity was evaluated using acetic acid induced writhing, formalin induced hind paw licking and thermally induced pain in mice. Acetyl salicylic acid (100 mg/kg) was used as the standard drug. The treatment dose ranges was 37-111 mg/kg. They reported that in the carrageenan induced edema model the extract exerted significant effect at the early stage of the inflammation (1-2 hours), indicating effect on histamine, kinins and serotonin and also reported the possibility of inhibition of prostaglandin release in the later stage of the inflammation. The result obtained from egg albumin induced edema model revealed that the extract blocks the histamine and 5-HT release. The extract shows significant activity in all the three models. The formalin test reports that it inhibits biphasic pain reaction, acts both centrally as well as peripherally. While the thermally induced pain model confirms that it acts also centrally. The anti-nociceptive activity can be attributed to the presence of secondary metabolites like saponins, terpenes, tannins, flavonoids [9].

2. *Abutilon indicum*

R.Saraswathi et al studied the analgesic and anti-inflammatory activity of the *Abutilon indicum*.
Phytochemical investigation shows the presence of components like sugars, saponins, flavonoids, alkaloids, glycosides, amino acids, phenolic compounds, tannins. Pentazocine (4 mg/kg) was used as the standard for the analgesic activity, while the diclofenac sodium (10 mg/ kg) was used as the standard for anti-inflammatory activity. The pet ether, chloroform, aqueous and ethanolic extracts were evaluated for their activities at the dose of 400 mg/kg. Analgesic activity was evaluated using Tail Flick method while the anti-inflammatory activity was evaluated using the Carrageenan induced paw edema model. Among the four extracts the methanolic and aqueous extracts were found to possess the little higher activity in both models [10].

3. *Crossopteryx febrifuga*

B. A. Chindo et al. reported Analgesic and anti-inflammatory activity of the methanolic extract of *Crossopteryx febrifuga*. Secondary metabolites tests reported the presence of alkaloids, tannins, saponnins, flavonoids, glycosides anthraquinones, carbohydrates, free reducing sugar, combined reducing sugars monossacharides, tannins, combined terpenes and phenols. Acetic acid induced paw edema model in mice and analgesymeter (Model 7200, Ugo, Basile, Italy) were employed to know the anti-nociceptive potential. Hind paw edema model in rats was used for the evaluation of anti-inflammatory activity. Acetyl salicylic acid (150 mg/kg) was used as the standard. The test extract was evaluated at the doses of 25, 50, 100 mg/kg. The significant reduction in acetic acid-induced writhes by this extract suggests that the analgesic effect may be peripherally mediated via the inhibition of synthesis and release of PGs (Koster et al., 1959) and other endogenous substances. The analgesymeter antinociceptive test suggests that significant increase in the pain threshold produced by the extract in the analgesymeter test suggests involvement of central pain pathways [11].

4. *Cussonia paniculata*

Adeolu A. Adedapo et.al. evaluated analgesic and anti-inflammatory activity of *Cussonia paniculata* stem bark. The aqueous extract of the bark at 50, 100 and 200 mg/kg significantly reduced the formation of oedema induced by carrageenan and histamine when compared to the standard drugs indomethacin (10 mg/kg) and cyproheptadine (10 mg/kg). The extract caused dose-dependent decrease of licking time and licking frequency in rats injected with 2.5% formalin, signifying its analgesic effect. Phytochemical screenings had shown that triterpene glycosides were isolated from the leaves of *C. paniculata*. Anti-inflammatory activities of many plants have been attributed to their high sterol/triterpene or flavonoids contents. Acute toxicity test showed that extract caused 80% mortality in rats at the dose of 400mg/kg and above reporting that it is a toxic plant [12].

5. *Oscillatoria willei*

Methanolic extract of *Oscillatoria willei* was investigated by hot plate and acetic acid induced writhing method to evaluate its analgesic activity while carrageenan induced hind paw edema and cotton pellet induced granuloma method was used to assess the anti-inflammatory action of the extract. The extract was evaluated at the dose of 50, 100, 200 mg/kg for both the activities. Morphine (2 mg/kg) was used as the standard drug for analgesic activity while indomethacin (10 mg/kg) was used for the assessment of anti-inflammatory activity. Analgesic action increases in a dose dependent manner. Extract showed maximum inhibition of 55.85% at the dose of 200 mg/kg after 3 h of drug treatment in carrageenan induced paw oedema model (acute model) while the standard drug showed 61.65% of inhibition. In the chronic model (cotton pellet induced granuloma), the extract (200 mg/kg) and standard drug had shown decreased formation of granuloma tissue of 52.92% and 56.48% (p < 0.001) respectively [13].

6. *Stereospermum kunthianum*

The analgesic activities of the compounds isolated from *Stereospermum kunthianum* were studied using the Randall-Selitto and formalin induced pain tests. At the dose of 20 mg/kg, Stereostin, Stereospermin (p<0.0001) and Stereospermiside (p<0.05) significantly reduced the carrageenan-induced pain with percentage pain inhibition of 73.7 % ,68.9 % and 37.4 % respectively compared to the distilled water treated animals. Similarly at the same dose of 20 mg/kg these three compounds significantly (p<0.0001) inhibited both phases of pain induced by the formalin, with a more pronounced effect on the second phase than in the first phase. The percentage inhibition of pain in the second phase was found to be 49.7%, 61.4%, 63.2% for Stereostin, Stereospermin and Stereospermiside respectively. Morphine (10 mg/kg) was used as the standard for the Randall-Selitto model while indomethacin (10 mg/kg) was used as the standard for formalin induced pain model [14].

7. *Mondia whytei*

Analgesic and anti-inflammatory activities of 9-Hexacosene and Stigmasterol isolated from *Mondia whytei* was performed by Charles Githua Githinji et. al. Stigmasterol (15 mg/kg) and 9- hexacosene (30 mg/kg) significantly (p<0.05) Caused the inhibition of the chemical nociception induced by intraperitoneal acetic acid. Stigmasterol (7.5, 15, 30 and 100 mg/kg) found to reduce the time spent in pain behavior in both the early and late phases of the formalin test in dose dependent manner. On the other hand 9-hexacosene caused significant (p<0.001) antinociceptive effect on the late phase of the formalin test in dose dependent manner. It was

predicted that stigmasterol acted as a neurosteroid. 9-hexacosene, an unsaturated hydrocarbon with a double bond at C-9 has structural resemblances to endoperoxides. So it was predicted that 9-hexacosene enters into the cyclo-oxygenase enzyme tunnel and because of its similarity with the normal substrate (endoperoxides), 9-hexacosene may act as false substrate. Again it was found that naloxone failed to antagonize the antinociception produced by neither stigmasterol nor 9-hexacosene, it was thought that the observed analgesic effect is not mediated through opioid receptors [15].

8. *Pfaffia glomerata*

The anti-inflammatory and antinociceptive effects of the crude hydroalcoholic extract of *Pfaffia glomerata* roots was assessed in the carrageenan-induced rat paw edema and acetic acid induced writhing in mice at the doses of 100, 200 and 300 mg/kg. An anti-inflammatory dose effect response correlation of $r = 0.997$ and $Y = 11.67x + 0.02$ was found while no dose response was found for the antinociceptive activity. 100, 200 ad 300 mg/kg of the extract inhibited the formation of edemaby 46.3, 56.8 and 63.2%, respectively, 3 h after injection of the inflammatory stimulus. This result was quite similar to the one observed for the standard drug indomethacin at 5 mg/kg, which inhibited the edema by 71.1%. The extract at 100, 200, 300 mg/kg was effective in inhibiting the writhings in mice by 69.1, 66.4 and 74.1%, respectively. Again hot plate test was done to evaluate if the extract have any central analgesic effect. The results for the group-treated with the extract did not differ significantly from the result obtained for the negative control group. On the other hand, the group-treated with morphine (4 mg/kg, subcutaneously) showed a highly significant result. Thus it is assumed that the extract has no analgesic effect on the CNS that would contribute to its peripheral analgesic effect [16].

9. *Swertia chirata*

The ethanolic root extract of *Swertia chirata* was assessed for analgesic and anti-inflammatory activities in animal models. The anti-inflammatory activity and analgesic effect were evaluated using the carrageenan-induced rat paw edema model, the acetic acid-induced writhing test and the radiant heat tail-flick method in mice respectively. Diclofenac (25 mg/kg) was used as the standard drug for the anti-inflammatory activity while Aminopyrine (50 mg/kg, p.o.) and morphine (2 mg/kg, s.c.) were used for the standards for the analgesic activity in acetic acid induced model and radiant heat tail flick model respectively. In rat paw edema model induced by carrageenan, the extract was found to reduce significantly ($p<0.001$) the formation of edema at the 400 mg/kg dose level and showed 57.81% ($p<0.001$) inhibition of edema volume at the end of 3 h. In the acetic acid-induced writhing test in mice, the extract at 200 and 400 mg/kg doses level showed 41.76% ($p<0.001$) and 58.29% ($p<0.001$) inhibition of writhing, respectively. In radiant heat tail-flick method, the root extract produced 43.88% ($p<0.001$) and 64.81% ($p<0.001$) increase in reaction time 30 min after oral administration at the 200 and 400 mg/kg doses level, respectively [17].

10. *Kigelia Africana*

Probable mechanism of analgesic and anti-inflammatory activity was evaluated for the ethanolic extract of *Kigelia Africana* using acetic acid induced mouse writhing and hot plate reaction time in mice for analgesic activity and carrageenan induced paw edema method in guinea pigs. Aspirin (100 mg/kg) was used as the standard drug for analgesic activity while indomethacin (10 mg/kg) was used as the standard drug for evaluation of anti-inflammatory activity. Extract was taken at 100, 200 and 500 mg/kg b.w.. The inhibitory effect produced by the ethanolic extract was greatest at the 3rd hour and lasted till the 5th hour and highest dose 500 mg/kg exhibited higher activity. In the writhing assay, the extract caused a significant (p<0.0001) inhibition of the number of writhes while extracts failed to increase mice reaction time on hot plate method. When compared with the indomethacin (10 mg/kg) the % inhibition shown by the extract was 98% at second hour, 94.8% at third hour and 85% of that of indomethacin at the fifth hour. However, higher effect was observed at the 30th min, first and fourth hour as the % inhibition produced by the extract was 156.8, 112.6 and 105.6% of the standard drug indomethacin. Thus it was reported that the plant is useful in the treatment of rheumatism and other ailments in which inflammation is implicated (Watt and Breyer-Bradwijk,1962). From the result obtained from the inhibition of acetic acid-induced writhing in mice it can be suggested that the analgesic effect of the extracts may be peripherally mediated via the inhibition of the synthesis and release of prostaglandins (Koster et al., 1959). As the extract failed to increase the pain threshold in the hot plate method, it was suggested that analgesic effect of the plant is not centrally mediated [18].

10. *Microtrichia perotitii* DC

Leaves of the *Microtrichia perotitii* DC was studied for its analgesic and anti-inflammatory activities using the the n-butanol phase of the methanolic extract. In the analgesic studies acetic acid writhing test in mice was used because of its sensitivity that could provide different grades of noxious stimuli in chemically induced tissue damage. The formaldehyde (2.5% v/v) induced inflammation in rats was used for the evaluation of anti-inflammatory activity. Proxicam 10 mg/kg was used as the standard drug for analgesic and ketoprofen (10 mg/kg, i.p.) was used as the standard drug for anti-inflammatory activity. Three doses levels 25, 50, 100 mg/kg were used for the evaluation of the activities. The percentage inhibition was found to be highest at the lowest dose (25 mg/kg) and was closely followed by the highest dose(100 mg/kg), both of which were remarkably higher than the standard drug used (Proxicam 10 mg/kg). In anti-inflammatory studies, the results obtained showed a significant reduction in the oedema formation. Values were higher than that of ketoprofen [19].

11. *Anisopus mannii*

The methanolic extract of the aerial parts of *Anisopus mannii* was evaluated for its analgesic activity by acetic acid-induced abdominal constriction test in mice and anti-inflammatory activities by carrageenan induced paw oedema in rats. Ketoprofen (10 mg/kg) was used as the standard drug in both cases. Extracts was studied at 20 and 40 mg/kg b.w.. The extract at doses of 20 and 40 mg/kg significantly (P < 0.05) reduced the number of abdominal constriction by 32.40 and 56.3% respectively while standard drug produced 48.9% reduction in abdominal constriction. At the 2nd hour extract at the lower dose 20 mg/kg showed inhibition of 52.2% compared to 65.2% for ketoprofen. The extract was reported to possess peripheral mediated analgesic activity as the

abdominal constriction response is thought to involve in part local peritoneal receptors and proposed that it may decrease the release of prostaglandins and lipooxygenase. As the Carrageenan induced inflammation is believed to be biphasic, early phase (1 - 2 h) is mainly mediated by histamine, serotonin and prostaglandins in the damaged tissue surroundings. Late phase is sustained by prostaglandins released and mediated by leukotrienes, bradykinin, polymorphonuclear cells and prostaglandins produced by tissue macrophages (Brito and Antonio, 1988). As the anti-inflammatory activity was similar to tha NSAIDs, it was suggested that that it acts in later phase probably involving arachidonic acid metabolites which produce oedema dependent on neutrophils mobilization [20].

12. *Securinega virosa*

The methanolic root bark extract of *Securinega virosa* was tested for the anti-inflammatory activity by carrageenan-induced rat paw oedema model. The analgesic activity was evaluated by acetic acid-induced writhing and hot plate method in Swiss albino mice, and by formalin-induced pain in Wistar rats. The extract was tested for both activities at the doses of 6.25, 12.5, 25 mg/kg b.w.. Standard drugs used for the comparision were piroxicam (10 mg/kg for acetic acid induced writhing), morphine sulphate (5 mg/kg b.w. for themally induced pain), morphine sulphate (4 mg/kg for formalin induced pain) and ketoprofen (10 mg/kg for carrageenan induced paw oedema method). In case of acetic acid induced writhing model highest inhibition of abdominal constriction (P < 0.01) observed at 25 mg/kg which was greater than that of piroxicam (P < 0.01). The formalin induced pain is biphasic. Drugs that act primarily on the CNS inhibit both phases in equal manner but peripherially acting drugs inhibit only the later phase (Chan etal., 1995). The highest inhibition was obtained at 12.5 mg/kg but at the highest dose 25 mg/kg; the extract significantly (P < 0.05) inhibited the inflammatory pain. The effects was not dose dependent.The suppression of both phases was observed in this study suggests the involvement of both central and peripheral effects with greater effect on neurogenic pain. In hot plate method, the ability of the extract to increase the pain threshold further suggested central analgesic activity with the reaction time at the dose of 12.5 mg/kg (14.2 ± 1.61) was found to be twice that of the untreated group.Significant inhibition of the paw oedema was observed in a dose dependent manner. The anti-inflammatory effect of the extract at the highest dose at the end of the third hour was 52% compared to 60% for ketoprofen [21].

13. *Zizyphus rugosa*

The water, chloroform, ethyl acetate and methanolic extracts of root barks of *Zizyphus rugosa* were evaluated for their anti-inflammatory and analgesic activities. The anti-inflammatory activity of extracts was tested by carrageenan-induced paw edema method in rats and analgesic activity by acetic acid induced writhing in mice. The treatment doses for aqueous extract were 50, 100 and 200 mg/kg; while chloroform, methanolic and ethyl acetate extracts were evaluated at 200 mg/kg. Aspirin was used as the standard drug for comparison for both the models. Again piroxicam (5 mg/kg) was also used as the standard drug for anti-inflammatory activity. The i.p. administration of the aqueous extract of the plant (50, 100 and 200mg/kg) reduced significantly the paw edema by 37.81%, 69.18% and72.90%

respectively three hours. While the i.p. administration of the methanolic extract had shown the inhibition by 67.57%. No significant activity was observed with the chloroform and ethyl acetate extracts. Standard drugs aspirin and piroxicam reduced the paw oedema by 70.27% and 54.54%, respectively at the third hour. On acetic acid-induced writhing model, a dose-dependent effect was observed after i.p. administration of the aqueous extract (50,100 and 200 mg/kg) with a significant decrease of writhing by 37.82%, 64.39% and 71.57%. Other extracts were ineffective. Aspirin inhibited 63.35% of the number of writhing [22].

14. *Solanum Trilobatum* Linn

Methanolic Root Extract of *Solanum Trilobatum* Linn was evaluated for its analgesic by hot plate and acetic acid induced writhing methods while it was also evaluated for its anti-inflammatory activity using carrageenan, and cotton pellet induced granuloma tests. Acute and chronic inflammation models were followed in rats and analgesic models in mice. Pentazocine (5 mg/kg s.c.) and indomethacin (10 mg/kg) were the standard drugs for analgesic activity. Dexomethasine (o.5 mg/kg) and indomethacin (10 mg/kg) were used as the standard drugs for the comparison of the anti-inflammatory activity. Methanolic extracts at 10, 100, 200, 300 mg/kg were tested for both the activities. The doses of 100, 200 and 300 mg/kg significantly (p<0.01) inhibited oedema formation 3 hrs after carrageenan challenge as well as cotton plate granuloma formation. Maximum % inhibition of writhing responses exhibited by the extract at 300 mg/kg was found to be 46.68%, while at 200 and 100 mg/kg it was found to be 44.58% and 32.53% reduction that was comparable to that of standard indomethacin 73.73%. The highest nociperception of thermal stimulus was exhibited at a higher dose 300 mg/kg of the extract (62.78%) that was comparable with the standard pentazocine (72.91%). As significant activity was obtained in both of the anti-inflammatory models, it was suggested that the extract is useful both in acute and chronic inflammation. The results obtained from the analgesic models suggest that the extract exhibit its analgesic effect by both peripheral and central nervous mechanisms [23].

15. *Anogeissus acuminata*

Methanolic extract of *Anogeissus acuminata* leaf were reported for its analgesic analgesic and anti-inflammatory effect. The anti-inflammatory effect was evaluated in carrageenan-induced paw oedema in wistar albino rats and formalin-induced paw oedema in Swiss albino mice. The activity was compared with the standard indomethacin (5 mg/kg). The analgesic effect was tested in Swiss albino mice by Eddy's hot plate method and was compared with the standard aspirin (25 mg/kg). The methanolic extract was evaluated in two different doses of 200 and 400 mg/kg. significant inhibition of inflammation (p≤0.01) was observed in the carragenan induced paw oedema in rat at both doses. At 200 mg/kg dose, 66.67% inhibition and at 400 mg/kg dose, 77.78% inhibition was observed and was comparable with the standard drug indomethacin 88.89% at the end of 3hrs. Significant inhibition was also observed in the formalin induced paw oedema in mice and Hot plate method at both doses [24].

Conclusion

The various extracts of above discussed plants are found to have significant analgesic and anti-inflammatory activity in different type of study models. The models used for the study of analgesic activity are: acetic acid induced writhing; formalin induced pain, thermally induced pain, heat tail flick method etc.

The acetic acid induced writhing model is regarded as a very sensitive method that uses minimal noxious stimulus; even weak analgesics can be detected with this test [25]. In this model, pain is generated indirectly via endogenous mediators like bradykinin, histamine, substance P, serotonin and prostaglandin, which stimulated peripheral nociceptive neurons. The abdominal constriction response induced by acetic acid is a sensitive procedure to evaluate peripherally acting analgesics [12]. Acetic acid induced writhing is a simple, rapid and reliable model to evaluate the peripheral type of analgesic action of herbal and other drugs [26]. However, the results of writhing test alone could not ascertain whether the anti-nociceptive effect was centrally or peripherally mediated.

The formalin test was carried out to confirm the centrally and peripherally mediated analgesic activity. The test consists of two phases that can be separated in time. The first phase or early phase involves direct effect of formalin on nociceptors, whereas the late phase involves inflammatory pain attributable to prostaglandin synthesis. The formalin test is more useful model of clinical pain in which the late phase was dependent on peripheral inflammation and changes in central processing. The histamine, serotonin, prostaglandins, nitric oxide and bradykinin are involved in the late phase of the formalin test [27]. Centrally acting drugs inhibit both phases of formalin-induced pain while peripherally acting drugs only inhibit the late phase. The effect of the extract on tail flick response provides a confirmation of its central effect since the assay is specific for opioid induced analgesic effect [28].

Tail flick and hot plate tests are the tests of nociception which are based on a phasic stimulus of high intensity. Pain induced by thermal stimulus of the hot plate is specific for centrally mediated nociception. The ability of the extract to prolong the latency to thermally-induced pain suggests central analgesic activity [21].

Carrageenan-induced paw edema as an *in vivo* model of inflammation is the most frequently used method to evaluate the anti-edematous effect of natural products [22].

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