ASSESSMENT OF ANTIPYRETIC ACTIVITY OF OPERCULINA TURPETHUM LINN SILVA

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ABSTRACT: *The present study was conducted to evaluate the antipyretic activity of the ethanolic extract of* **Operculina turpethum** *(Linn.) Silva Manso, a traditional medicinal plant known for its wide therapeutic applications in Ayurvedic medicine. The investigation was carried out using the 20% turpentine induced pyrexia model in Wistar albino rats. Pyrexia was induced by subcutaneous injection of 20% aqueous suspension of 20% turpentine and rectal temperatures were recorded at regular intervals. The animals were divided into six groups: control, Diseased, standard (aspirin (100mg/kg), and three test groups receiving ethanolic extract of* **O. turpethum** *at doses of 150 mg/kg , 200 mg/kg and 250 mg/kg orally. The results demonstrated a significant reduction in rectal temperature in the groups treated with the plant extract, particularly at the higher dose, when compared to the control group (p<0.05). The antipyretic effect was comparable to that of paracetamol, indicating the potential of* **O. turpethum** *as a natural antipyretic agent. The observed activity may be attributed to the presence of bioactive constituents such as flavonoids, phenolics, and glycosides, known for their antipyretic properties. This study supports the traditional use of* **Operculina turpethum** *in the treatment of fever and encourages further pharmacological and phytochemical investigations to isolate the active compounds responsible for the antipyretic activity.*
Keywords: antipyretic, fever, operculina turpethem inn silva

I. INTRODUCTION

Fever refers to an increase in body temperature beyond the regulatory set point of 36.5 -37.5 $^{\circ}$C (98- 100° F). This increase in temperature triggers muscle tone and shivering. Fever signifies several illnesses. Symptoms of fever include sweating, chills, a sensation of cold and other subjective sensations. The absence of these symptoms when the temperature is high can be a pointer to a serious illness[1]. Fever may be caused by infections caused by parasites, viruses, bacteria and immune reactions (including defects in collagen, immunological abnormalities and acquired immunodeficiency[2]. Fever can also be a result of the destruction of tissues during trauma, local necrosis (infarction), an inflammatory reaction in tissues and vessels (flebitis, arthritis), pulmonary infarction, and rhabdomyolysis[3].

In humans, temperature regulation is controlled by the thermoregulatory center in the hypothalamus[4]. The input to the hypothalamus comes from peripheral as well as central thermo-receptors. Research has revealed neural substrates for thermoregulatory control[5]. The peripheral and central thermoreceptors situated beneath the skin are of two subtypes namely those that respond to cold and those responding to warmth[6]. The warm central thermo receptors are located in the hypothalamus, spinal cord, viscera, and great veins, which are more numerous than cold thermo-receptors[7].

Pain is an unpleasant sensory affliction and emotional experience usually associated with actual or potential tissue damage or described in terms of such damage[8]. Pain serves as a warning signal against disturbances. Pain is aimed at protecting the organism but often leads to discomfort[9]. We have two types of pain nociceptive and pathological pain. Nociceptive pain is also known as acute pain, which usually accompanies noxious stimuli warning of impending tissue damage[10].

Pathological pain, according to its cause, is divided into inflammatory pain and neuropathic pain, both belong to chronic pain[11]. Chronic pain completes the list of largest medical health problems in countries with many low-income cadres of people[12]. Treatment of pain and related problems calls for a good understanding of how pain signals are initially interpreted and subsequently transmitted and perpetuated[13].

Antinociceptive such as opiates and non-steroidal anti-inflammatory drugs (NSAIDs) have many side effects[14]. Pain studies, treatment and management have made important progress now, but remain underestimated and poorly managed mostly in developing countries[15]. This leads to pain among hospitalized patients is extensive, and

significantly more[16].

Inflammation is a major cause of morbidity today. If poorly managed, inflammation may become complicated leading to the development of rheumatoid arthritis, diabetes, cancer, Alzheimer's disease, and atherosclerosis along with pulmonary, autoimmune and cardiovascular diseases[17]. Inflammation is a response of living tissue to injury[18]. Inflammation may be referred to as innate immunity. It may appear due to microbial infections, physical factors (trauma, radiation, temperature), chemical substances (irritant and corrosive chemicals), as well as tissue necrosis and hypersensitivity reactions[19]. It is didactically characterized by redness, heat, swelling, pain and dysfunction of the organs involved[20].

The search for new drugs is ongoing. Research on plant-based drugs used as alternative and complementary medicine is of great interest because they are cheap, have fewer side effects and are readily available[21]. Although a considerable number of drugs are available for the treatment of fever, pain and inflammation, there is a continuous search for new compounds as therapeutic alternatives, because these drugs exert a wide range of side effects and low efficacy, especially for chronic diseases[22].

Pain, fever and inflammation are managed using conventional drugs such as diclofenac, Ibuprofen, morphine, acetylsalicylic acid (ASA) and acetaminophen[11]. Non-steroidal anti-inflammatory drugs are frequently prescribed analgesics[23]. For they are a highly effective drug for the management of fever, pain and inflammation; however, NSAIDs are known to have multiple adverse effects, including gastrointestinal bleeding, cardiovascular side effects, and NSAID induced nephrotoxicity[24]. NSAIDs reduce pain by inhibiting COX enzymes and reducing prostaglandin synthesis[24]. Natural products have been one of the most successful sources of new therapeutic agents[25]. Alternative and complementary therapy form a better option for they are cheap and readily available. Medicinal plants formed an integral part of human society to combat different diseases at the beginning of human civilization[26]. Herbal plants are a good source of phytochemicals that have many therapeutic potentials.

Medicinal plants contain pharmacologically active chemicals that can be used to cure diseases[27,29].
Medicinal plants form an integral part of human society to combat different diseases at the beginning of human civilization[26]. Herbal plants are a good source of many types of phytochemicals which have many therapeutic potentials. The term phytochemical has its origin in the Greek word phyto, which means plant[30]. The secondary metabolites are biologically active compounds[31]. Medicinal plants are useful and many contain phytocompounds that can be used to cure diseases[27]. For instance, nicotine is from the tobacco plant while cocaine is extracted from the coca plant (*Erythroxylum coca*) while (*Nicotiana tabacum*), 9-tetrahydro- cannibinol (THC) comes from the marijuana plant (*Cannabis sativa*), similarly, the well-known pain killer morphine is obtained from opium poppy plant (*Papaver somniferum*), the precursor for the synthesis of aspirin salicylic acid is extracted from the bark of the willow tree (*Salix nigra*) and (*Salix alba*)[28].

Phytochemicals are found in plants leaves, stems, barks, flowers, fruits and roots. Phytochemicals are categorized into two main groups namely primary and secondary metabolites based on the kind of function they have in plant metabolism[32]. Proteins, amino acids, pyrimidines, purines, Chlorophyll, and Sugars form the primary metabolites while terpenes, phenolics, alkaloids, steroids, saponins, flavonoids and glycosides form the secondary metabolites[33].

Phytochemicals protect plants from harsh environmental hazards like predation, stress, drought, UV exposure and attack by pathogens[34]. They form an important source of information that is useful in drug development in pharmaceutical industries[35]. Studies have shown that terpenoids have several pharmacological benefits that are useful in the treatment of inflammatory, cancer, malaria, viral infections and many bacterial infections[36]. Phenolics are the most abundant group of phytochemicals in medicinal[37] plants.
Dietary phenolics constitute flavonoids, phenolic acids, and polyphenols. A diet that is rich in Polyphenol possesses several health benefits namely improvement of cardiac function, decrease anginas and lowers cholesterol levels[38]. Flavonoids also reduce the production of pathogenic thrombosis in mice models. Alkaloids are used as analgesic agents and are found in medicinal plants[39].

In Embu County, Kenya, several medicinal plants are used in the management of fever, pain and inflammation. These include *Eucalyptus globulus* (Labill) and *Senna didymobotrya* (Fresenius). *E. globulus* is used in the treatment of bronchitis, cancer, arthritis, asthma, boils, cold, cough, diabetes, dysentery, dyspepsia, malaria, sore

throat, tuberculosis, vaginitis and wounds[40] while *S. didymobotrya* pharmacological activities include treatment of skin infections, malaria, ringworm, jaundice, intestinal worm, bacterial infections, fungal, sickle cell anemia, haemorrhoids and hypertension[41]. However, there is no scientific information available in the literature to validate their biological activities. Therefore, this study seeks to carry out quantitative phytochemical screening, antipyretic, analgesic and anti-inflammatory potential of leaf extracts of *E. globulus* and *S. didymobotrya*.

II. MATERIALS AND METHODS

Collection and preparation of plant materials
Fresh plant aerial part of the selected plant was collected from Ranga Reddy District, Hyderabad, and Telangana. These plants are believed by the locals to have medicinal value against various ailments. The plant materials were identified by Dr. Madhava Chetty, Asst. Professor, Sri Venkateshwara University, Tirupati, Andhra Pradesh the collected plant part was first washed 2−3 times using tap water, to remove adherent particles and dried under shade for com. Preparation of plant extracts was carried out using a protocol as described by Nostro *et al*. (2000).[42] the dried material was ground to a fine powder using a grinder and passed through a mesh sieve. The powdered materials were kept at room temperature away from direct sunlight in closed dry khaki paper bags.

Extraction
The coarse powder of aerial Operculina turpethum (Linn.) Silva Manso was packed tightly in the soxhlet apparatus and extracted with ethanol for 72 hours with occasional shacking maintained at 60ºc throughout the extraction process. The extract was concentrated to of its original volume by evaporation. The resulting ethanolic extract of aerial Operculina turpethum (Linn.) Silva Manso was subjected to phytochemical study.

Procurement of animals
Male swiss albino rats, weighing 100-150 g were purchased from the, Jeeva life sciences, Hyderabad. Animals were housed 5 per cage, allowed access to water and food, ad libitum, and maintained at a constant temperature of $22 \pm 2°C$ and humidity of 50-55% and 12 h of light/dark cycle. All experimental procedures were carried out by the Institutional Animal Ethics Committee affiliated with CCSEA.

Experimental design
Experimental rats were split into six groups of five animals each (n = 5).
Group I (normal control) comprised normal rats that were administered with 3% DMSO.
Group II (negative control) comprised rats that had been induced with pyrexia using 20% turpentine. They were administered with 3% DMSO.
Group III (positive control) comprised turpentine-induced pyretic rats that were administered with aspirin (100mg/kg bw).
Group IV comprised of turpentine induced pyretic rats that were administered with extract dose of 150mg/kg bw.
Group V comprised turpentine induced pyretic rats that were administered with extract dose of 200mg/kg bw
Group VI comprised of turpentine induced pyretic rats that were administered with extract dose of 250mg/kg body weight.

The body temperature of rats in all the groups was taken after fever induction and at hourly intervals following administration of treatments for four hours[43]. Approximately 3cm of a well-lubricated digital thermometer (thermistor probe®) was inserted into the anal region of the rats to measure the rectal temperature[44]. The thermistor animals in the experimental group were taken using both types of thermometers and compared.
The thermostor probe® was first quantified against a mercury thermometer, where temperatures of the animals in the experimental groups were recorded using both thermometers and compared. The baseline/initial mean rectal temperature was calculated by measuring the rectal temperature of rats at fifteen minutes intervals for 1 hour before the induction of fever.
The rectal temperatures of rats were measured and recorded at hourly intervals for 4 hours after the administration of different treatments. The rats whose rectal temperatures rose by one degree Celsius one hour after intraperitoneal injection of turpentine (20mg/kg bw) were termed pyretic and were used for the studies. The difference in rectal temperatures before and after treatments was obtained and the % inhibition in the rectal temperature computed according to the formula as described by Hukkeri *et al.,* 2006; Yemitan and Adeyemi, 2017.[45,46]

$$\% \ inhibition \ of \ pyrexia = \frac{B - C_n}{B} \times 100$$

Where,

B - Rectal temperature at one hour following turpentine injection
Cn - Rectal temperature after treatments.

III. RESULT AND DISCUSSION

Pharmacological evaluation
Antipyretic activity
The extract of Operculina turpethum (Linn.) Silva Manso generally exhibited *in vivo* antipyretic activities in rats, which was evidenced by a reduction in rectal temperature against turpentine induced fever. After one hour of treatment, the groups of Swiss albino rats that received aspirin (100mg/kg body weight) and the extract doses of 150, 200 and 250 mg/kg bw lowered the rectal temperature to 97.05%, 97.11%, 96.55% and 96.69% respectively.

The Operculina turpethum (Linn.) Silva Manso extract dose of 200 caused the highest antipyretic activity, which reduced pyrexia by 2.43% in the first hour. This change was higher than that caused by the reference drug, aspirin, which reduced pyrexia by 1.93%. However, the effect of aspirin was comparable to that of extracts dose levels of 150, 200 and 250 ($p > 0.005$).

In the 2nd hour, the Operculina turpethum (Linn.) Silva Manso extract reduced the elevated rectal temperature in a dose-dependent fashion. At doses of 150, 200 and 250, the extract lowered the raised rectal temperature to 95.91%, 95.77% and 95.72% respectively (Table 6.2). The antipyretic activities of the leaf extract doses of 150 and 200 were statistically similar and comparable to that of aspirin ($p < 0.005$; Table 6.2).

In the 3rd hour post-treatment, the leaf extract doses of 150, 200 and 250 lowered the elevated rectal temperature in rats to 95.35%, 95.12%, 95.39% respectively (Table 6.2). Similarly, at this hour the extract showed a dose-independent antipyretic potential. The rats that received the Operculina turpethum (Linn.) Silva Manso extract at doses of 150, 200 and 250 exhibited antipyretic activities that were significantly different ($p < 0.005$; Table 6.2). However, the antipyretic activity of aspirin was statistically similar compared to that of the extract at all tested dose levels ($p > 0.005$; Table 6.2).

In the 4th hour, the Operculina turpethum (Linn.) Silva Manso extract reduced raised rectal temperature in a dose-dependent manner. The extract of *Operculina turpethum (Linn.) Silva Manso doses* of 150, 200 and 250 reduced pyrexia to 94.52%, 94.17%, 94.15%, respectively (Table 6.2). At this hour, the group that received extract of *Operculina turpethum (Linn.) Silva Manso at* a dose of 250 recorded the highest antipyretic effects, which was higher than that of aspirin (Table 6.2). The antipyretic effects of the extract doses of 150, 200 and 250 were not significantly different from each other and were comparable to that of the reference drug, aspirin ($p > 0.005$; Table 6.2).

Notably, the animals in the normal control group showed no remarkable change in rectal temperature from zero to the fourth hour (p>0.005). However, the animals in the negative control group had a significant increase in rectal temperature from hour zero to hour three (p<0.005). On the other hand, there was a significant reduction in rectal temperature of rats that were treated with aspirin and *Operculina turpethum (Linn.) Silva Manso* extract at all the doses tested from hour zero to the fourth hour (p<0.005).

Antipyretic effects of *Operculina turpethum (Linn.) Silva Manso* on turpentine-induced pyrexia in rat

Group	Treatment	Percentage change in rectal temperatures (°C)				
		0hr	**1hr**	**2hr**	**3hr**	**4hr**
Group I	3% DMSO	100.00±0.00	99.87±0.13a (0.11)	100.12±0.22a (-0.16)	99.72±0.13a (0.22)	99.88±0.18a (0.11)

Group		0hr	1hr	2hr	3hr	4hr
Group II	Turpentine + DMSO	100.00±0.00	100.41±0.06a (-0.42)	100.11±0.10a (-0.57)	100.65±0.18b (-0.68)	100.51±0.12a (-0.52)
Group III	Turpentine + Aspirin	100.00±0.00	97.05±0.07cd (1.93)	96.52±0.15bc (2.45)	95.81±0.12cde (3.18)	94.29±0.16d (4.69)
Group IV	Turpentine + 150 mg/kg bw	100.00±0.00	97.11±0.15cd (1.87)	95.91±0.05cd (3.06)	95.35±0.09e (3.63)	94.52±0.07cd (4.47)
Group V	Turpentine + 200 mg/kg bw	100.00±0.00	96.55±0.10d (2.43)	95.77±0.06cd (3.20)	95.12±0.08e (3.87)	94.17±0.07d (4.80)
Group VI	Turpentine + 250mg/kg bw	100.00±0.00	96.69±0.05d (2.29)	95.72±0.07d (3.27)	95.39±0.05e (3.59)	94.15±0.10d (4.83)

Values are expressed as mean ± SEM for 5 rats per group. Values with different superscript letters are statistically significant ($p \leq 0.005$) along the same column. The figures in brackets represent mean % inhibition.

Percentage change in rectal temperatures (ºC)
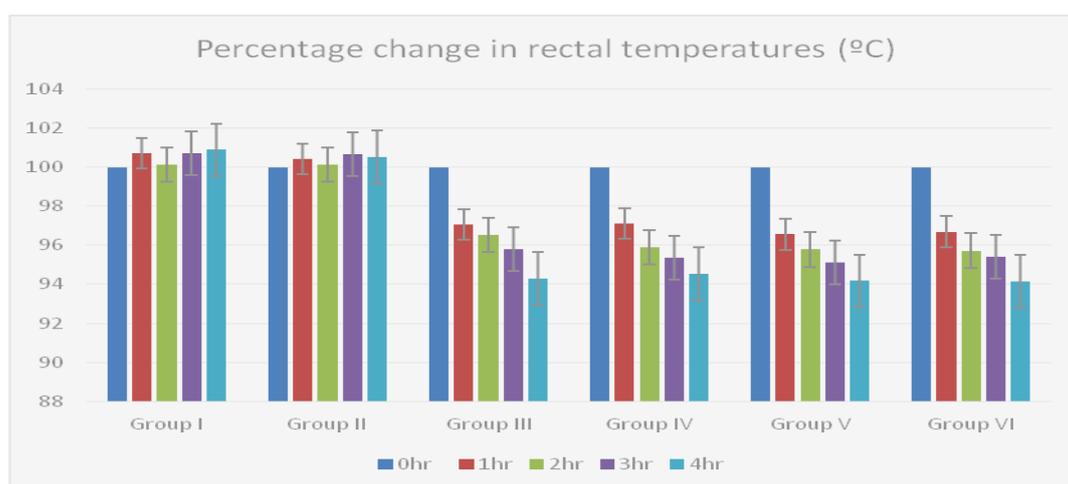
Discussion

Turpentine induced pyrexia is a preferred model for antipyretic studies for its quick and reliable way of testing for fever, for example, as opposed to yeast induced fever model which takes 18-24 hours after administration for pyrexia to be induced[47]. The current study aimed at evaluating the antipyretic activities of aerial part of *Operculina turpethum (Linn.) Silva Manso on* turpentine-induced fever in Swiss albino rats. Upon bio-screening for the antipyretic activities of extracts of aerial part of *Operculina turpethum (Linn.) Silva Manso on* turpentine-

induced fever in Swiss albino rats, the results showed that fever was remarkably reduced at all extract doses. The ethanolic extract of aerial part of *Operculina turpethum (Linn.) Silva Manso at* the doses of 250mg/kg bw, exhibited the highest rectal temperature reduction which compared well with the reference drug, aspirin. The150mg/kg bw was not effective compared to those of higher doses of 200 and 250. This could be due to the rapid metabolism, clearance and inactivation of the lower concentration of the bioactive agents or chemical modification in the body (biotransformation) where the drug loses biological activity[48].

Generally, the NSAIDs produce their antipyretic action via prostaglandin biosynthesis inhibition within the hypothalamic pre-optic region[49]. It has been conceptualized that a leak in the blood-brain barrier at the level of the OVLT permits the CNS to sense the presence of endogenous pyrogens[50]. Other mechanisms that have been conceptualized include active transport of cytokines into the OVLT or cytokine receptors activation in endothelial cells of the neural vasculature, which then transducer signals to the brain[51]. It is, therefore, possible that the extract of aerial part of *Operculina turpethum (Linn.) Silva Manso has* a similar mechanism of action to that of aspirin through prostaglandin biosynthesis inhibition in the hypothalamus.

The results in this study indicated that varying doses have different antipyretic potentials. The present study used dose ranges of 150, 200 and 250 mg/kg BW. The extracts of aerial part of *Operculina turpethum (Linn.) Silva Manso at* all the tested doses of 150, 200 and 250, never lowered rectal temperatures in the 1st and 2nd hours as effectively as in the 3rd and 4th hours. These findings could be due to the biotransformation of active agents in the extract to become antipyretic. The intraperitoneal route of drug administration provides a relatively slow onset of drug effects because the drug takes time to diffuse across the membrane and interact with the drug receptors. On the other hand, most of the absorbed drug agents enter the portal circulation and there may be significant inactivation of the active compounds before they reach the desired sites of action[52].

The extracts of aerial part of *Operculina turpethum (Linn.) Silva Manso dose* of 200 was marginally more effective than aspirin. These findings suggest a better or a similar prostaglandin synthesis inhibition by the active components in the plant extracts. There is, therefore, the possibility of the plant extracts working effectively by blocking alternative mechanisms of cox-2 or prostaglandin E-2 synthesis during fever inhibition.

The anti-pyretic effects of extracts of aerial part of *Operculina turpethum (Linn.) Silva Manso may* be due to their phytochemicals observed in preliminary phytochemical screening. The extracts showed a dose-independent response with a dose level of 250mg/kg BW having the highest antipyretic activity. The present study supports the traditional use of these plants in the management of fever.

CONCLUSIONS

This study revealed that the *Operculina turpethum (Linn.) Silva Manso* extracts possess potent antipyretic activities. The study also revealed that the effects of plant extract at doses of 200 and 250mg/kg bodyweight were comparable with that of the reference drugs, aspirin and diclofenac. The synergistic and additive effects of the bioactive constituents increase their bioavailability and action on multiple molecular targets thus, the observed activities of *Operculina turpethum (Linn.) Silva Manso extract* is attributed to secondary metabolites they contain. This study, therefore, confirms and supports the use of the studied plant extracts as an alternative and/or complementary remedy against pain and fever. The study also sets the pace for further studies in an effort to develop plant-derived drug compounds for the treatment of fever. From this study, it is concluded that; i. The ethanolic extract of aerial part of *Operculina turpethum (Linn.) Silva Manso has* several phytochemical agents associated with antipyretic activity in rats.

REFERENCES

1. Székely, M. and Garai, J. (2018). Thermoregulation and age. In Handbook of clinical neurology, 156, 377-395. Elsevier.
2. Tohidpour, A., Morgun, A. V., Boitsova, E. B., Malinovskaya, N. A., Martynova, G. P., Khilazheva, E. D. and Salmina, A. B. (2017). Neuroinflammation and infection: molecular mechanisms associated with dysfunction of neurovascular unit. Frontiers in Cellular and Infection Microbiology, 7, 276.
3. Anochie, I. P. (2013). Mechanisms of fever in humans. International Journal of Microbiology and Immunology Research, 2 (5), 37-43.
4. Barbi, E., Marzuillo, P., Neri, E., Naviglio, S. and Krauss, B. S. (2017). Fever in children: pearls and pitfalls. Children, 4(9), 81-100.
5. Cabral, A., Valdivia, S., Reynaldo, M., Cyr, N. E., Nillni, E. A. and Perello, M. (2012). Short-term cold exposure activates TRH neurons exclusively in the hypothalamic paraventricular nucleus and raphe pallidus. Neuroscience letters, 518(2), 86-91.
6. Ward, J. P. and Linden, R. W. (2017). Physiology at a Glance. John Wiley & Sons
7. Patel, M. D., Patel, J. H., Rajput, M. B. and Bariya, A. R. (2016). Adaptive physiological and biochemical responses of dairy animals to heat stress: a review. International Journal of Applied and Natural Sciences, 5(1), 107-116.

8. Srilakshmi, D. and Sachchidananda, S. G. (2018). World Journal of Pharmaceutical Sciences. World, 6(6), 112-115.

9. Singh, A., Klapper, A., Jia, J., Fidalgo, A., Tajadura-Jiménez, A., Kanakam, N. and Williams, A. (2014). Motivating people with chronic pain to do physical activity: opportunities for technology design. In Proceedings of the SIGCHI Conference on Human Factors in Computing Systems , 2803- 2812.

10. Rio, E., Moseley, L., Purdam, C., Samiric, T., Kidgell, D., Pearce, A. J. and Cook, J. (2014). The pain of tendinopathy: physiological or pathophysiological?. Sports medicine, 44(1), 9-23.

11. Díaz-Rodríguez, L., García-Martínez, O., Morales, M. A., Rodríguez-Pérez, L., Rubio-Ruiz, B. and Ruiz, C. (2012). Effects of indomethacin, nimesulide, and diclofenac on human MG-63 osteosarcoma cell line. Biological research for nursing, 14(1), 98-107.

12. Gelband, H., Sankaranarayanan, R., Gauvreau, C. L., Horton, S., Anderson, B. O., Bray, F., and Gupta, S. (2016). Costs, affordability, and feasibility of an essential package of cancer control interventions in lowincome and middle-income countries: key messages from Disease Control Priorities. The Lancet, 387(10033), 2133-2144.

13. Dimitroulas, T., Duarte, R. V., Behura, A., Kitas, G. D. and Raphael, J. H. (2014). Neuropathic pain in osteoarthritis: a review of pathophysiological mechanisms and implications for treatment. In Seminars in arthritis and rheumatism.W.B Saunders. 44(2), 145-154).

14. Hogans, B. B. and Barreveld, A. M. (Eds.). (2019). Pain Care Essentials. Oxford University Press.

15. Porta-Sales, J., Nabal-Vicuna, M., Vallano, A., Espinosa, J., Planas-Domingo, J., Verger-Fransoy, E. and Grimau, I. (2015). Have we improved pain control in cancer patients? A multicenter study of ambulatory and hospitalized cancer patients. Journal of Palliative Medicine, 18(11), 923- 932.

16. Franceschi, F., Marsiliani, D., Alesi, A., Mancini, M. G., Ojetti, V., Candelli, M. and Proietti, R. (2015). A simplified way for the urgent treatment of somatic pain in patients admitted to the emergency room: the SUPER algorithm. Internal and emergency medicine, 10(8), 985-992.

17. Patil, K. R., Mahajan, U. B., Unger, B. S., Goyal, S. N., Belemkar, S., Surana, S. J. and Patil, C. R.(2019). Animal Models of Inflammation for Screening of Anti-inflammatory Drugs: Implications for the Discovery and Development of Phytopharmaceuticals. International Journal of Molecular Sciences, 20(18), 4367.

18. Eming, S. A., Wynn, T. A. and Martin, P. (2017). Inflammation and metabolism in tissue repair and regeneration. Science, 356(6342), 1026- 1030.

19. Silva, L. (2015). A literature review of inflammation and its relationship with the oral cavity. Global Journal of Infectious Diseases and Clinical Research, 1(2), 21-7.

20. Actor,J. K., and Smith,K.C.(2019).Translational Inflammation. In Translational Inflammation. (1-22). Academic Press.

21. Reid, A. M., Oosthuizen, C. B., Fibrich, B. D., Twilley, D., Lambrechts, I. A., de Canha, M. N. and Lall, N. (2018). Traditional Medicine: The Ancient Roots of Modern Practice. In Medicinal Plants for Holistic Health and Well-Being (1-11). Academic Press.

22. Calogero, A. E., Condorelli, R. A., Russo, G. I. and La Vignera, S. (2017). Conservative nonhormonal options for the treatment of male infertility: antibiotics, anti-inflammatory drugs, and antioxidants. BioMed research international, (2017),1-17.

23. Abdulla, A., Adams, N., Bone, M., Elliott, A. M., Gaffin, J., Jones, D. and Schofield, P. (2013). Guidance on the management of pain in older people. Age and ageing, 42, 151-157.

24. Wongrakpanich, S., Wongrakpanich, A., Melhado, K., and Rangaswami, J. (2018). A comprehensive review of non-steroidal anti-inflammatory drug use in the elderly. Aging and disease, 9(1), 143.

25. David, B., Wolfender, J. L. and Dias, D. A. (2015). The pharmaceutical industry and natural products: historical status and new trends. Phytochemistry Reviews, 14(2), 299-315.

26. Kooti, W., Moradi, M. T., Ali-Akbari, S., Sharafi-Ahvazi, N., Asadi-Samani, M. and Ashtary-Larky, D. (2014). Therapeutic and pharmacological potential of Foeniculum vulgare Mill: a review. Journal of HerbMed Pharmacology, 4(1), 1-9.

27. Daniel, M. (2016). Medicinal plants: chemistry and properties. CRC Press.

28. Rai, S. K. and Tewari, A. K. (2018). Dual role of drugs: beneficial and harmful aspects. In Synthesis of Medicinal Agents from Plants. 305-332. Elsevier.

29. Kaur, A., Umar, A. and Kansal, S. K. (2016). Heterogeneous photocatalytic studies of analgesic and non-steroidal anti-inflammatory drugs. Applied Catalysis A: General, 510, 134-155.

30. Fazilah, N. F., Ariff, A. B., Khayat, M. E., Rios-Solis, L. and Halim, M. (2018). Influence of probiotics, prebiotics, synbiotics and bioactive phytochemicals on the formulation of functional yogurt. Journal of functional foods, 48, 387-399.

31. Fiorito, S., Epifano, F., Palmisano, R., Genovese, S. and Taddeo, V. A. (2017). A re-investigation of the phytochemical composition of the edible herb Amaranthus retroflexus L. Journal of pharmaceutical and biomedical analysis, 143, 183-187.

32. Jain, C., Khatana, S. and Vijayvergia, R. (2019). Bioactivity of secondary metabolites of various plants: a review. International Journal of Pharmaceutical Sciences and Research, 10(2), 494-498.

33. Alamgir, A. N. M. (2018). Secondary metabolites: secondary metabolic products consisting of C and H; C, H, and O; N, S, and P elements; and O/N heterocycles. In Therapeutic Use of Medicinal Plants and their Extracts.(2) 165-309): Spring Cham

34. Das, S. K., Patra, J. K. and Thatoi, H. (2016). Antioxidative response to abiotic and biotic stresses in mangrove plants: A review. International Review of Hydrobiology, 101(1-2), 3-19.

35. Böttger, A., Vothknecht, U., Bolle, C. and Wolf, A. (2018). Plant Secondary Metabolites and Their General Function in Plants. In Lessons on Caffeine, Cannabis & Co, Springer, Cham, 3-17.

36. Kabera, J. N., Semana, E., Mussa, A. R. and He, X. (2014). Plant secondary metabolites: biosynthesis, classification, function and pharmacological properties. Journal of Pharmacognosy and Pharmacology, 2, 377-392.

37. Zaynab, M., Fatima, M., Abbas, S., Sharif, Y., Umair, M., Zafar, M. H. and Bahadar, K. (2018). Role of secondary metabolites in plant defense against pathogens. Microbial pathogenesis, 124, 198-202.

38. Baião, D. D. S., De Freitas, C. S., Gomes, L. P., Da Silva, D., Correa, A. C. N., Pereira, P. R. and Paschoalin, V. M. F. (2017). Polyphenols from root, tubercles and grains cropped in Brazil: Chemical and nutritional characterization and their effects on human health and diseases. Nutrients, 9(9), 1044-1073.

39. Dembitsky, V. M. (2014). Naturally occurring bioactive Cyclobutane-containing (CBC) alkaloids in fungi, fungal endophytes,

and plants. Phytomedicine, 21(12), 1559-1581.

40. Dixit, A., Rohilla, A. and Singh, V. (2012). Eucalyptus globulus: A new perspective in therapeutics. International journal of pharmaceutical and chemical sciences, 1, 1678-1683.

41. Maobe, M. A. G. M. (2014). Standardization of Selected Medicinal Herbs from Kisii Region Used in Treatment of Diabetes, Malaria and Pneumonia (Doctoral dissertation).

42. Nostro A, Germanò MP, D'angelo V, Marino A, Cannatelli MA. Extraction methods and bioautography for evaluation of medicinal plant antimicrobial activity. Lett Appl Microbiol. 2000 May;30(5):379-84. doi: 10.1046/j.1472-765x.2000.00731.x. PMID: 10792667.

43. Wan, J., Gong, X., Jiang, R., Zhang, Z. and Zhang, L. (2013). Antipyretic and anti- inflammatory effects of asiaticoside in lipopolysaccharide- treated rat through up- regulation of heme oxygenase- 1. *Phytotherapy Research*, *27*(8), 1136-1142.

44. Nthiga, P. M., Kamau, J. K., Safari, V. Z., Mwonjoria, J. K., Mburu, D. N. and Ngugi, M. P. (2016). Antipyretic Potential of Methanolic Stem Bark Extracts of *Harrisonia Abyssinica* Oliv and *Landolphia Buchananii* (Hallier F.) Stapf in Wistar Rats. *Journal of Applied Pharmacology*, *8*(3),1-7.

45. Hukkeri, V.I., Nagathan, C.V. and Karadi, R.V. (2006). Antipyretic and wound healing activities of *Moringa oeifera* in rats. *Indian Journal of Pharmaceutical Sciences,* 68: 124-32.

46. Yemitan, O. K. and Adeyemi, O. O. (2017). Mechanistic assessment of the analgesic, anti-inflammatory and antipyretic actions of *Dalbergia saxatilis* in animal models. *Pharmaceutical biology*, *55*(1), 898-905.

47. Vanitha, L. (2008). *Anti inflammatory Analgesic Anti pyretic study on Pavazhamalli Ilai Chooranam (Nyctanthes arbortristis. Linn) and Anti fungal Study on Kutta Chooranam* (Doctoral dissertation, Government Siddha Medical College, Palayamkottai).

48. Yang, Y., Zhang, Z., Li, S., Ye, X., Li, X. and He, K. (2014). Synergy effects of herb extracts: pharmacokinetics and Pharmacodynamic basis. *Fitoterapia*, *92*, 133-147

49. Habib, M. and Waheed, I. (2013). Evaluation of anti-nociceptive, antiinflammatory and antipyretic activities of Artemisia scoparia hydromethanolic extract. *Journal of Ethnopharmacology*, *145*(1), 18- 24.

50. Dantzer, R. (2017). Neuroimmune interactions: from the brain to the immune system and vice versa. *Physiological reviews*, *98*(1), 477-504.

51. Yeo, D. C., Wiraja, C., Mantalaris, A. S. and Xu, C. (2014). Nanosensors for regenerative medicine. *Journal of biomedical nanotechnology*, *10* (10), 2722-2746.

52. Al-Salihi, B. (2016). Ma Huang (Ephedrae Herba): setting the record straight. *Journal of Chinese Medicine*, *(110)* 18-30.