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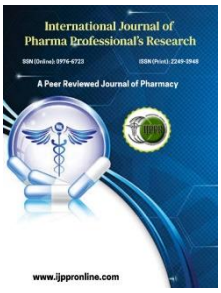

Paracetamol (N-acetyl-p-aminophenol, APAP) Threats: Therapeutic Clock

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ABSTRACT:

Paracetamol (acetaminophen) is without a doubt one of the most generally utilized drugs around the world. As a non-prescription drug, paracetamol is the norm and first-line treatment for fever and intense agony and is accepted to remain so for a long time to come. Notwithstanding being in clinical use for more than hundred years, the exact system of activity of this recognizable medication stays a secret. The most seasoned and most winning hypothesis on the system of pain relieving and antipyretic activities of paracetamol connects with the restraint of CNS cyclooxygenase (COX) protein exercises, with clashing perspectives on the COX isoenzyme/variation designated by paracetamol and on the idea of the atomic communications with these compounds. Paracetamol has been proposed to specifically hinder COX-2 by functioning as a decreasing specialist, notwithstanding the way that in vitro screens exhibit low power on the hindrance of COX-1 and COX-2. The component of paracetamol activity comprises in restraint of cyclooxygenases (COX-1, COX-2, and COX-3) and contribution toward the finish of cannabinoid framework and serotonergic pathways. Furthermore, paracetamol impacts transient receptor potential (TRP) channels and voltage-gated Kv7 potassium channels and restrains T-type Cav3.2 calcium channels. It additionally applies an effect on L-arginine in the nitric oxide (NO) amalgamation pathway. In any case, not these impacts have been obviously affirmed.

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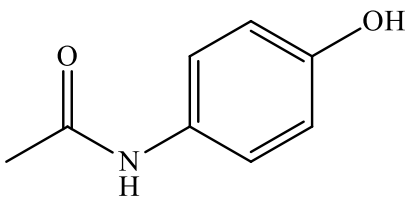
Introduction:

Historical Background of Acetaminophen

One of the most commonly used over-the-counter antipyretic pain relievers is paracetamol (acetaminophen, N-acetyl-p-aminophenol). Joseph von Mering originally performed it in 1893 by reacting p-nitrophenol with tin and chilly acidic corrosive. Paracetamol and phenacetin (Figure 1) were discovered to have antipyretic and later pain-relieving effects in the 1880s. At initially, phenacetin gained popularity over paracetamol and was advertised in 1887; however, due to major side effects such hemolytic pallor and methemoglobin arrangement, phenacetin's clinical use fell and attention turned to paracetamol, which was advertised in 1893. Although paracetamol (acetaminophen) was discovered in Germany near the end of the nineteenth century, it took until the middle of the twentieth century for it to become widely used. The dangers of over-the-counter medications

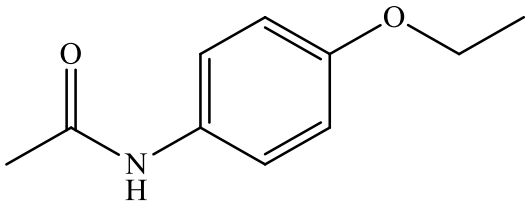
Utilization has increased across the board. Utilization grew fivefold in the Nordic countries between 1978 and 1988, but it decreased by 8 g/person/year in nations including the US, Canada, Australia, and New Zealand. In other recently developed nations, rates in 1994–1995 were 20 g/person/year. 2,3 According to estimates, the number of 500 mg pills consumed annually in the UK rose from 1500 million in 1967–1968 to 4,000 million in 1993–1994 2 3500 million 500 mg tablets totaling prescribed paracetamol, combination tablets, and paracetamol purchased without a solution were utilised in 2000 as a proxy for subsequent usage (IMS Wellbeing, Sheen unpublished information). Paracetamol was exempt from the stringent poisonousness testing that is conducted prior to presentation when medications are being produced.

i)



Acetaminophen

ii)



Phenacetine

Figure1: Acetaminophen along with Phenacetine.

Therapeutic Mechanism of Acetaminophen (Paracetamol)

Paracetamol is currently utilized in many structures either alone or in mix with different medications (normally sedatives) for absense of pain and in different combinations like cold 'remedies' for its pain relieving and antipyretic properties.

Analgesic action of paracetamol

Adults use paracetamol to treat a variety of severe painful conditions, such as migraine, outer muscular pain, menstrual pain, osteoarthritis pain in the back and neck, dental pain, and postoperative pain [6–13]. For adults, the usual dosage of paracetamol is 2 tablets, each containing 500 mg, which must be taken orally every hour up to a maximum of 8 pills in a 24-hour period. Paracetamol dosages for children are based on age and range from 60 mg (2–3 months) to 480–750 mg (long term olds). When combined with other painkillers such headache medication, caffeine, or some narcotic painkillers, paracetamol is sold as a single pharmacologically active synthetic chemical or

in plans [14,15]. The typical useful Which cyclooxygenase catalyst does paracetamol restrain?

Results of the COX-1 and COX-2 proteins, especially PGE2, have been displayed to play significant parts in the transmission of nociceptive agony at the destinations of agony commencement and furthermore at the spinal and supraspinal nociceptive pathways, hindrance of which has been exhibited to intervened the fringe and now and again focal pain relieving activities of NSAIDs. At long last, in 2002, Chandrasekharan et al found the third cyclooxygenase (COX-3) in canines and recommended that its demeanor could assume a part in the antipyretic impact of paracetamol.

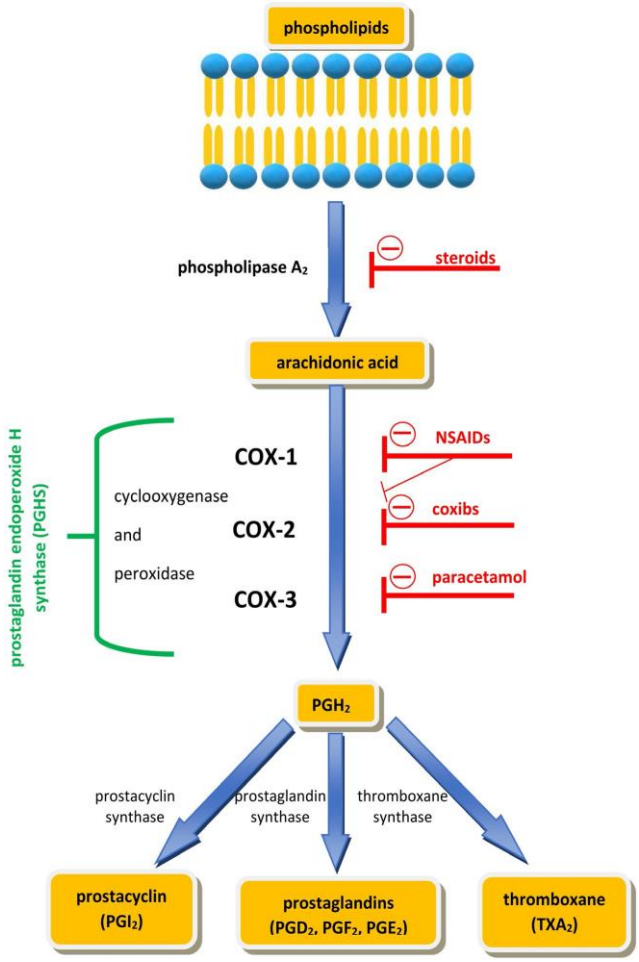


Figure 2: Simplified peripheral schematic diagram of arachidonic acid metabolism, showing that prostaglandin

endoperoxide-H synthase (PGHS) comprises of two proteins: a clinically more significant cyclooxygenase part and peroxidase. The transformation of AA includes first cyclization to unsound 15-hydroxyperoxide (PGG2) by cyclooxygenase, and afterward the peroxidase (POX) action diminishes the created PGG2 to PGH2.

Accordingly, the point of our paper was to sum up the present status of information on the system of paracetamol activity.

Cyclooxygenases isoforms derived from PGs.

Prostaglandin Endoperoxide-H Synthase (PGHS), a bifunctional enzyme that, along with the peroxidase (POX) component, converts arachidonic acid (AA) into prostaglandin H2, depends on cyclooxygenases for its action (PGH2). 17 Arachidonic corrosive is extremely clearly oxygenated in the 11R design to begin the COX production of prostaglandin (PG), which is followed by a 15S oxygenation to form PGG2. The POX translocation then causes PGG2 to become PGH2. 17 Prostaglandin H undergoes additional modification by different tissue proteins into prostacyclin (PGI2), thromboxanes A2 and B2 (TXA2 and TXB2, separately), prostaglandins of the D (PGD2), E (PGE2), and F (PGF2) families, and prostacyclin.

A constitutive substance, COX-1 is permanently transmitted in numerous tissues, primarily the kidneys and the gastrointestinal mucosa[21,22]. As a result, frequent administration of large NSAID dosages reduces the development

Diverse Significances of COX-3

Understanding the effects of some commonly used antipyretic and painkillers, notably the effect of paracetamol, was greatly enhanced by the discovery of COX-3. Although Chandrasekharan et al. suggested that COX-3 might eventually have similar components

of activity to that of the recently discovered isoforms, it also seems to have a few other distinct recognisable characteristics[16,32].

Sub-atomic cloning's use in the discovery of COX-3 in a canine has already sparked a lot of inquiries[20]. The declaration of COX-3 was the primary remarkable quality. Although COX-3 is translated from a comparable quality as the recently discovered COX-1, it produces a variety of polypeptides that are very sensitive to painkillers and antipyretics but have minimal mitigating effects.

MECHANISMS O F C OX-3 I NHIBITION

The proposed hypotheses of COX-3 association in the enlistment of fever and agony are muddled. The main errors showed up subsequent to considering investigations of the chemical delivering prostanoids, which underlie fever development[35]. After erasure of the COX-2 quality however not the COX-1 quality in mice, the fever blunted[36]. This proposes that the prostanoid-delivering chemical is related with neither the COX-1 protein nor the COX-1 quality, which, significantly, additionally encodes COX-3. Fever reaction is unequivocally connected with a fast enlistment of COX-2 articulation and expanded PGE2 creation, with no job for COX-1 or a COX-1 quality item (eg, COX-3)[41]. Subsequently, COX-2-specific inhibitors pitifully affecting COX-1 and COX-3 are as great at diminishing fever as conventional NSAIDs[36-39]. The COX-3 hypotheses began declining after it had created the impression that COX-3, so delicate to paracetamol in canines, doesn't serve such a capability in the human organism[46]. In any case, a canine COX-3 simple unquestionably exists in the organic entity of people and rodents, particularly in the focal sensory system (CNS)[40]. To affirm this, 24 cDNAs of COX-1 were cloned from the human cerebral cortex. In all clones, intron 1 of human COX-1 is 94-nucleotide long, subsequently moving the leftover succession of human COX-3 out of casing versus the open perusing edge of COX-1[41].

Paracetamol and TRP channels

Transient receptor potential (TRP) channels have a place with a 28-protein superfamily, which can be separated into seven subfamilies[42]. TRP channels are professed to be polypeptide subunits that gather as tetramers to shape cation-penetrable pores. By tweaking intracellular calcium levels[43], TRP channels assume significant parts as transduction particles, answering different physical and substance specialists (change in shear pressure, osmolarity, pH, temperature, responsive atoms, and different specialists) in the intracellular and extracellular milieu.104 Problems of the elements of these channels exist together with hereditary sicknesses: skeletal, skin, tangible, visual, heart, and neuronal disturbances. By obliterating the flagging capability of tactile neurons[44], For example, intrathecal RTX infusion in canines experiencing osteosarcoma torment, emphatically diminished torment behavior[45]. Thusly, it is likely that the pain relieving activity of paracetamol is additionally interceded by TRPV1 channels and cannabinoid CB1 receptors, which are both present in the torment and thermoregulatory pathways.88,114-116 Extra signs of the collaboration of CB1 and TRPV1 diverts in the CNS in paracetamol-prompted absense of pain have been recommended in the concentrate by Fioravanti et al in 2008[46]. It was shown that AM404-prompted absense of pain was missing in TRPV1-/ - mice and was likewise nullified by an intra cerebro ventricular infusion of capsazepine, which is a TRPV1 antagonist. Strangely, there are mind regions where FAAH (which structure the AM404 metabolite) is profoundly communicated within the sight of both CB1 and TRPV1 channels (mesencephalic trigeminal core, essential tangible neurons).118-120 Other than the

mind, FAAH is additionally communicated in the spinal rope and dorsal root ganglia.

In any case, the pace of AM404 arrangement in the last two regions was a lot of lower than in the mind in indistinguishable trial conditions.88 This appears to verify the hypothesis proposed by Hammer et al that paracetamol manages TRPV1 at the supravertebral level.94 Sadly, late examinations have confounded the issue of the significance of TRP diverts in the paracetamol activity. Andersson et al portrayed that co-articulation of various TRP directs happens in the nociceptive tangible neurons, and the pain relieving impact of paracetamol furthermore happens by enacting another subfamily, ie subfamily A (ankyrin 1) of transient receptor potential (TRPA1) channels[47]. TRPA1 is communicated in the soma and fringe sensitive spots of the tactile neurons and is answerable for distinguishing destructive stimuli[48-50] Like TRPV1, TRPA1 answers an uncommonly wide assortment of compound stimuli, eg mustard oil, cannabinoids, garlic, and cinnamaldehyde. The synthetic enactment of TRPA1 causes torment, disturbance, and hyperreactivity in skin and instinctive organs, through decrease of voltage-gated calcium and sodium flows in essential tactile neurons[51-58].

All the more significantly, TRPA1 receptors are actuated additionally by different metabolites of paracetamol: the electrophilic N-acetyl-p-benzoquinoneimine (NAPQI) and p-benzoquinone (p-BQ). This was affirmed by an intrathecal test where NAPQI, p-BQ, and the electrophilic TRPA1 activator cinnamaldehyde delivered antinociception that was lost in TRPA1−/−mice in a hot-plate test. These paracetamol metabolites are shaped in the liver with contribution of such chemicals as monooxygenase, peroxidase, and COX of cytochrome P450 (CYP450)[59-61].

Strangely, large numbers of these chemicals are available in the CNS.133,134 NAPQI is accepted to cause the notable hepato-and nephrotoxic impacts of paracetamol. In any case, NAPQI metabolites can be seen as in human and mouse blood, pee, or even spinal string after ingestion of remedial and non-harmful portions of this drug[62-64]. These discoveries show the intricacy of paracetamol digestion[64]. It has for quite some time been realized that TRPV1 directs control internal heat level in vivo; for instance, agonists, for example, capsaicin and RTX prompt the hypothermic impact in rodents. In this manner, TRPV1 enactment may likewise underlie the hypothermic impact of paracetamol, however concentrates on mice showed that paracetamol-prompted hypothermia was indistinguishable in wild-type and Trpv1−/− mice and didn't diminish by organization of a maximally viable portion of a TRPV1 bad guy. Conversely, a TRPA1 bad guy repressed paracetamol-prompted hypothermia, and paracetamol had no impact on internal heat level in Trpa1−/− mice.61 As respects the COX-1 and COX-2 inhibitory movement of paracetamol, the hypothermic components give off an impression of being free of the cannabinoid framework; in any case, the antipyretic impact may likewise be a consequence of COX hindrance in the nerve center by AM404.

In this way, it would be fascinating not exclusively to make sense of the job of TRPV4 in the pain relieving/antipyretic impact of paracetamol, yet in addition to research the impact of paracetamol utilized for different purposes like cardiovascular homeostasis [65].

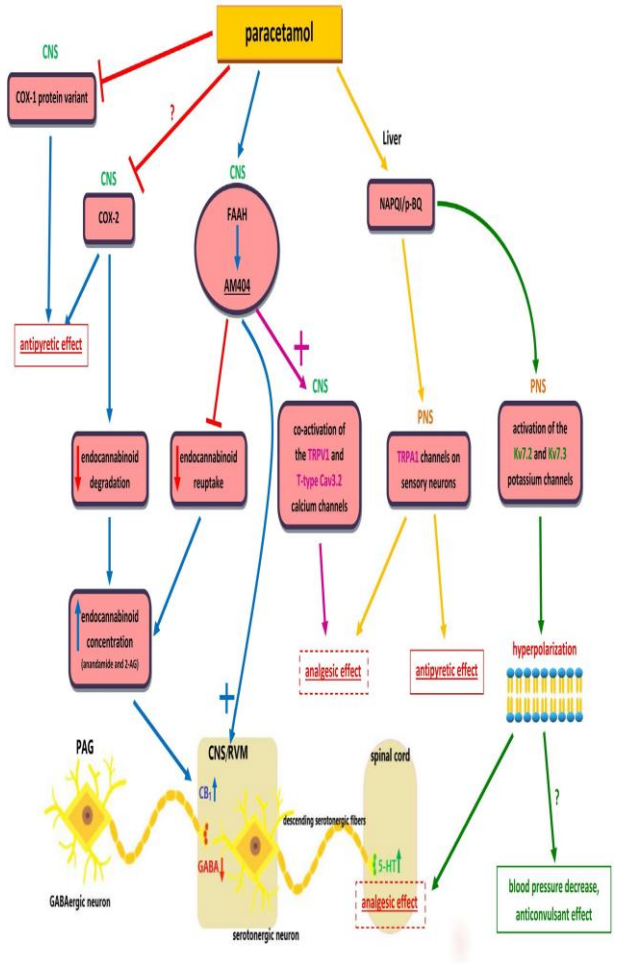


Figure:3 Speculative situation of paracetamol activity in focal sensory system (CNS) and liver. 2-AG, 2-arachidonoylglycerol; 5-HT, 5-hydroxytryptamine receptor (serotonin receptor); AM404, N arachidonoyl phenolamine; CB1, cannabinoid receptor type 1; CNS, focal sensory system; FAAH, greasy amide hydrolase; NAPQI, cN-acetyl-p-benzoquinoneimine; p-BQ, p-benzoquinone; PAG, periaqueductal dark; PNS, fringe sensory system; RVM, rostral ventromedial medulla; TRPA1, transient receptor potential subfamily ankyrin 1; TRPV1, transient receptor potential subfamily vanilloid-1.

Nitric oxide pathway in paracetamol action

After hurtful upgrades, enactment of spinal N-methyl-D-aspartate receptors (NMDARs) and arrival of substance P connected with the transmission of torment data occur[66-70]. Thus, research on mice has shown that the initiation of NMDARs advances the combination of nitric oxide (NO), which is a synapse at the spinal level passing on nociceptive information[71]. The proposed elective instruments of the pain relieving activity of paracetamol likewise incorporate impedance with initiation of spinal NMDARs and restraint of the NO pathway[72]. Organization of L-arginine (yet not D-arginine) represses the pain relieving impact of paracetamol. This proposes that the pain relieving impact of paracetamol might be related with hindrance of NO generation[73-76].

Paracetamol impact on Kv7 potassium channels

As of late, it has been depicted that NAPQI improves the movement of neuronal voltage-gated Kv7 potassium channels, Kv7.2 and Kv7.3, in dorsal root ganglion and spinal dorsal horn neurons [77-85]. In the phone culture climate of spinal dorsal horn societies of Sprague-Dawley rodents, by upgrading Kv7 channel action, NAPQI brings out hyperpolarization of the layer potential and diminishes activity possible terminating, which could underlie the pain relieving activity of paracetamol and add to paracetamol anticonvulsant properties[78-81]. Besides, immediate and roundabout enactment of Kv7 channels by NAPQI diminishes blood vessel tone, which can prompt a drop in blood vessel circulatory strain. This might be liable for the clinical peculiarity of intravenous paracetamol-subordinate transient hypotension [86-93]. This is another promising examination field that ought to be investigated in future exploration.

CONCLUSIONS AND FUTURE PERSPEC TIVES

Paracetamol is a for the most part used, unobtrusively fruitful aggravation easing and antipyretic. In overabundance it causes tremendous dismalness and mortality. The load to clinical consideration organizations is huge, with a high financial cost and various crisis center affirmations. Despite various

extensive stretches of assessment, the specific arrangement of paracetamol action stays dark. It is decidedly multidirectional, yet more assessment is supposed to explain it totally. Energy research eventual outcomes of the instrument of paracetamol movement are incredibly reassuring. Besides, they have arranged for the ascent of new analgesics and antipyretics that could act unequivocally through the serotonergic and endo-cannabinoid systems, TRP channels, Kv7 potassium channels, Cav3.2 calcium channels, or even a yet dark protein variety of COX-1.

References

1. Bertolini A, Ferrari A, Ottani A, Guerzoni S, Tacchi R, Leone S. Paracetamol: new vistas of an old drug. CNS Drug Rev. 2006;12(3–4):250-275.

2.Prescott LF. Paracetamol (Acetaminophen): A Critical Bibliographic Review, 1st edn. London, Taylor & Francis,1996.

3. Spooner JB, Harvey JG. The history and usage of paracetamol. J Int Med Res 1976; 4:1–6.

4. Newson RB, Shaheen SO, Chinn S, Burney PG. Paracetamol sales and atopic disease in children and adults: an ecological analysis. Eur Respir J 2000; 16:817–23.

5. Thomson JS, Prescott LF. Liver damage and impaired glucose tolerance after paracetamol overdosage. Br Med J 1966; 2:506–7.

6. Woo WW, Man SY, Lam PK, et al. Randomized double-blind trial comparing oral paracetamol andoral nonsteroidal anti-inflammatory drugs for treating pain after musculoskeletal injury. Ann Emerg Med. 2005;46(4):352–361.

7. Pendergrass PB, Scott JN, Ream LJ, et al. Effect of small doses of aspirin and acetaminophen on total menstrual loss and pain of cramps and headache. Gynecol Obstet Invest. 1985;19(1):32–37.

8. Hochberg MC, Dougados M. Pharmacological therapy of osteoarthritis. Best Pract Res Clin Rheumatol. 2001;15(4):583–593.

9. Porter RW, Ralston SH. Pharmacological management of back pain syndromes. Drugs. 1994;48 (2):189–198.

10. Dionne RA, Campbell RA, Cooper SA, et al. Suppression of postoperative pain by preoperative administration of ibuprofen in comparison to placebo, acetaminophen, and acetaminophen plus codeine. J Clin Pharmacol. 1983;23:37–43.

11. Haglund B, Von Bültzingslöwen I. Combining paracetamol with a selective cyclooxygenase-2 inhibitor for acute pain relief after third molar surgery: a randomized, double-blind, placebo-controlled study. Eur J Oral Sci. 2006;114(4):293–301.

12. Dahl V, Raeder JC. Non-opioid postoperative analgesia. Acta Anaesthesiol. Scand. 2000;44:1191–1203.

13. HKH L, SM T, FL L. A randomised control trial comparing the efficacy of tramadol and paracetamol against ketorolac and paracetamol in the management of musculoskeletal pain in the emergency department. J Emerg Crit Care Med. 2008;15(1):5–11.

14 Moore RA, et al. Minimum efficacy criteria for comparisons between treatments using individual patient meta-analysis of acute pain trials: examples of etoricoxib, paracetamol, ibuprofen, and ibuprofen/paracetamol combinations after third molar extraction. Pain. 2011;152(5):982–989.

15. Flower RJ, Vane JR. Inhibition of prostaglandin synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetamidophenol). Nature. 1972;240:410–411.

16. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature New Biol.1971;231:232–235.

17. Feldberg W, Gupta KP, Milton AS, et al. Effect of bacterial pyrogen and antipyretics on prostaglandin activity in cerebrospinal fluid of unanaesthetised cats. BrJ Pharmacol. 1972;46:550P-551P.

18. Yaksh TL, Malmberg AB. Spinal actions of NSAIDs in blocking spinally mediated hyperalgesia: the role of cyclooxygenase products. Agents Actions. 1993;41:89–100.

19. Malmberg AB, Yaksh TL. Capsaicin-evoked prostaglandin E2 release in spinal cord slices: relative effect of cyclooxygenase inhibitors. Eur J Pharmacol. 1994;271(2–3):293–299.[21] Muth-Selbach US, Tegeder I, Brune K, et al. Acetaminophen inhibits spinal prostaglandin E2 release after peripheral noxious stimulation. Anesthesiology. 1999;91:231–239.

20. Ayoub SS, Botting RM, Goorha S, et al. Acetaminophen-induced hypothermia in mice is mediated by a prostaglandin endoperoxide synthase 1 gene-derived protein. Proc Natl Acad Sci U S A. 2004;101:11165–11169.

21. Ayoub SS, Colville-Nash PR, Willoughby DA, et al. The involvement of a cyclooxygenase 1 gene-derived protein in the antinociceptive action of paracetamol in mice. Eur J Pharmacol. 2006;538(1–3):57–65.

22. Derendorf H, Drehsen G, Rohdewald P. Cortical-evoked potentials and saliva levels as basis for the comparison of pure analgesics to analgesic combinations. Pharmacology. 1982;25(4):227–236.

23. Bromm B, Forth W, Richter E, et al. Effects of acetaminophen and antipyrine on non-inflammatory pain and EEG activity. Pain. 1992;50(2):213–221.

24. Pickering G, Kastler A, Macian N, et al. The brain signature of paracetamol in healthy volunteers: a double-blind randomized trial. Drug Des Devel Ther. 2015;9:3853.

25. Shetty N1, AK P, SV G, et al. Comparison of the effects of ibuprofen and acetaminophen on PGE2 levels in the GCF during orthodontic tooth movement: a human study. Prog Orthod. 2013;14:6.

26. Seppälä E, Laitinen O, Vapaatalo H. Comparative study on the effects of acetylsalicylic acid, indomethacin and paracetamol on metabolites of arachidonic acid in plasma, serum and urine in man. Int J Clin Pharmacol Res. 1983;3(4):265–269.

27. ClissoldS P. Paracetamol and phenacetin. Drugs. 1986;32(4): 46–59. Suppl.

28. Gwilt JR, Robertson A, Goldman L, et al. The absorption characteristics of paracetamol in man. J. Pharm Pharmacol.1963;15:445.

29. Chandrasekharan NV, Dai H, Roos KLT, et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/ antipyretic drugs: cloning, structure, and expression. Proc Natl Acad Sci USA. 2002;99(21):13926-13931.

30. Liu J, Seibold SA, Rieke CJ, Song I, Cukier RI, Smith WL. Prostaglandin endoperoxide H synthases: peroxidase hydroperoxide specificity and cyclooxygenase activation. J Biol Chem.2007;282(25):18233-18244.

31. Gabbs M, Leng S, Devassy JG, Aukema HM. Advances in our understanding of oxylipins. Am Soc Nutr. 2015;6:513-540.

32. Anderson BJ. Paracetamol (Acetaminophen): mechanisms of action. Paediatr Anaesth. 2008;18(10):915-921.

33. Hazarika I, Selvam P. Cyclooxygenase 3 inhibition: a probable mechanism of acetaminophen in human: a review. Res Rev A J Pharm Sci. 2015;53:23-29.

34. Crofford LJ. COX-1 and COX-2 tissue expression: implications and predictions. J Rheumatol Suppl. 1997;49:15-19.

35. Zidar N, Odar K, Glavac D, Jerse M, Zupanc T, Stajer D. Cyclooxygenase in normal human tissues - is COX-1 really a constitutive isoform, and COX-2 an inducible isoform? J Cell Mol Med. 2009;13(9b):3753-3763.

36. Lazzaroni M, Bianchi PG. Gastrointestinal side-effects of traditional non-steroidal anti-inflammatory drugs and new formulations. Aliment Pharmacol Ther. 2004;20(s2):48-58.

37. Rajakariar R, Yaqoob MM, Gilroy DW. COX-2 in inflammation and resolution. Mol Interv. 2006;6(4):199-207.

38. Kurumbail RG, Kiefer JR, Marnett LJ. Cyclooxygenase enzymes: catalysis and inhibition. Curr Opin Struct Biol. 2001;11(6):752-760.

39. Carnieto A, Dourado PMM, da Luz PL, Chagas ACP. Selective cyclooxygenase- 2 inhibition protects against myocardial damage in experimental acute ischemia. Clinics (Sao Paulo). 2009;64(3):245-252.

40.Ruan C-H, So S-P, Ruan K-H. Inducible COX-2 dominates over COX-1 in prostacyclin biosynthesis: mechanisms of COX-2 inhibitor risk to heart disease. Life Sci. 2011;88(1–2):24-30.

41. Patrignani P, Panara MR, Greco A, et al. Characterization of the cyclooxygenase activity of human blood prostaglandin endoperoxide synthases. Adv Prostaglandin Thromboxane Leukot Res. 1995;23(3):129-131.

42. Massó González EL, Patrignani P, Tacconelli S, García Rodríguez LA. Variability among nonsteroidal antiinflammatory drugs in risk of upper gastrointestinal bleeding. Arthritis Rheum. 2010;62(6):1592-1601.

43. Brune K, Patrignani P. New insights into the use of currently available non-steroidal anti-inflammatory drugs. J Pain Res. 2015; 8:105.

44. Li S, Ballou LR, Morham SG, Blatteis CM. Cyclooxygenase-2 mediates the febrile response of mice to interleukin-1β. Brain Res. 2001;910(1–2):163-173.

45. Li S, Ballou LR, Morham SG, Blatteis CM. Cyclooxygenase-2 mediates the febrile response of mice to interleukin-1β. Brain Res. 2001;910(1–2):163-173.

46. Simmons DL, Botting RM, Robertson PM, Madsen ML, Vane JR. Induction of an acetaminophen-sensitive cyclooxygenase with reduced sensitivity to nonsteroid antiinflammatory drugs. Proc Natl Acad Sci USA. 1999;96(6):3275-3280.

47. Warner TD, Mitchell JA. Cyclooxygenase-3 (COX-3): filling in the gaps toward a COX continuum? Proc Natl Acad Sci USA. 2002;99(21):13371-13373.

48. Oksuz E, Atalar F, Tanırverdi G, Bilir A, Shahzadi A, Yazici Z. Therapeutic potential of cyclooxygenase-3 inhibitors in the management of glioblastoma. J Neurooncol. 2016;126(2):271-278.

49. Aronoff DM, Neilson EG. Antipyretics: mechanisms of action and clinical use in fever suppression. Am J Med. 2001;111(4):304-315.

50. Kis B, Snipes JA, Isse T, Nagy K, Busija DW. Putative cyclooxygenase- 3 expression in rat brain cells. J Cereb Blood Flow Metab. 2003;23(11):1287-1292.

51. Sharma S, Verma A, Chauhan R, Kedar M, Kulshrestha R. Study of cyclooxygenase-3 on the bases of its facts and controversies. Int J Pharm Sci Res. 2019;10(1):387-392.

52. Li S, Wang Y, Matsumura K, Ballou L, Morham S, Blatteis C. The febrile response to lipopolysaccharide is blocked in cyclooxygenase-2−/−, but not in cyclooxygenase-1−/− mice. Brain Res. 1999;825(1–2):86-94.

53. Cao C, Matsumura K, Yamagata K, Watanabe Y. Endothelial cells of the rat brain vasculature express

cyclooxygenase-2 mRNA in response to systemic interleukin-1β: a possible site of prostaglandin synthesis responsible for fever. Brain Res. 1996;733(2):263-272.

54. Kurumbail RG, Stevens AM, Gierse JK, et al. Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory agents. Nature. 1996;384(6610):644-648.

55. Luong C, Miller A, Barnett J, Chow J, Ramesha C, Browner MF. Flexibility of the NSAID binding site in the structure of human cyclooxygenase- 2. Nat Struct Biol. 1996;3(11):927-933.

56. Riendeau D, Percival MD, Boyce S, et al. Biochemical and pharmacological profile of a tetrasubstituted furanone as a highly selective COX-2 inhibitor. Br J Pharmacol. 1997;121(1):105-117.

57. Riendeau D, Percival MD, Brideau C, et al. Etoricoxib (MK-0663): preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. J Pharmacol Exp Ther. 2001;296(2):558-566.

58. Dinchuk JE, Liu RQ, Trzaskos JM. COX-3: in the wrong frame in mind. Immunol Lett. 2003;86(1):121.

59. Botting R, Ayoub SS. COX-3 and the mechanism of action of paracetamol/ acetaminophen. Prostaglandins Leukot Essent Fatty Acids. 2005;72(2):85-87.

60. Schwab JM, Beiter T, Linder JU, et al. COX-3 - A virtual pain target in humans? FASEB J. 2003;17(15):2174-2175.

61. Pickering G, Loriot M, Libert F, Eschalier A, Beaune P, Dubray C. Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. Clin Pharmacol Ther. 2006;79(4):371-378.

62. Moran MM, McAlexander MA, Bíró T, Szallasi A. Transient receptor potential channels as therapeutic targets. Nat Rev Drug Discov. 2011;10(8):601-620.

63. Moran MM. TRP channels as potential drug targets. Annu Rev Pharmacol Toxicol. 2018;58(1):309-330.

64. Parenti A, De Logu F, Geppetti P, Benemei S. What is the evidence for the role of TRP channels in inflammatory and immune cells? Br J Pharmacol. 2016;173(6):953-969.

65. Zhang ZM, Wu X, Zhang G-Y, Ma X, He D-X. Functional food development: insights from TRP channels. J Funct Foods. 2019;56:384-394.

66. De Petrocellis L, Bisogno T, Davis JB, Pertwee RG, Di Marzo V. Overlap between the ligand recognition properties of the anandamide transporter and the VR1 vanilloid receptor: inhibitors of anandamide uptake with negligible capsaicin-like activity. FEBS Lett. 2000;483(1):52-56.

67. Brauchi S, Orta G, Mascayano C, et al. Dissection of the components for PIP2 activation and thermosensation in TRP channels. Proc Natl Acad Sci USA. 2007;104(24):10246-10251.

69. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature. 1997;389(6653):816-824.

70. Bandell M, Story GM, Hwang SW, et al. Noxious cold ion channel TRPA1 is activated by pungent compounds and bradykinin. Neuron. 2004;41(6):849-857.

71. Baraldi PG, Preti D, Materazzi S, Geppetti P. Transient receptor potential ankyrin 1 (TRPA1) channel as emerging target for novel analgesics and anti-inflammatory agents. J Med Chem. 2010;53(14):5085-5107.

72. Holzer P. Transient receptor potential (TRP) channels as drug targets for diseases of the digestive system. Pharmacol Ther. 2011;131(1):142-170.

73. Viana F. Chemosensory properties of the trigeminal system. ACS Chem Neurosci. 2011;2(1):38-50.

74. Prescott L, Critchley J, Balali-Mood M, Pentland B. Effects of microsomal enzyme induction on paracetamol metabolism in man. Br J Clin Pharmacol. 1981;12(2):149-153.

75. Dahlin DC, Miwa GT, Lu AYH, Nelson SD. N-acetyl-pbenzoquinon imine: a cytochrome P-450-mediated oxidation product of acetaminophen. Isotopenpraxis. 1984;20(1):1327-1331.

76. Hinson JA, Roberts DW, James LP. Mechanisms of acetaminophen- induced liver necrosis. Handb Exp Pharmacol. 2010;196:369-405.

77. Björkman R, Hallman KM, Hedner J, Hedner T, Henning M. Acetaminophen blocks spinal hyperalgesia induced by NMDA and substance P. Pain [Internet]. 1994;57(3):259-264.

78. Bujalska M. Effect of cyclooxygenase and no synthase inhibitors administered centrally on antinociceptive action of acetaminophen (Part II). Pol J Pharmacol. 2003;55(6):1001-1011.

79. Ryu YS, Lee JH, Seok JH, et al. Acetaminophen inhibits iNOS gene expression in RAW 264.7 macrophages: differential regulation of NF-κB by acetaminophen and salicylates. Biochem Biophys Res Commun. 2000;272(3):758-764.

80. Prado WA, Schiavon VF, Cunha FQ. Dual effect of local application of nitric oxide donors in a model of incision pain in rats. Eur J Pharmacol. 2002;441(1–2):57-65.

81. Smith WL, Malkowski MG. Interactions of fatty acids, nonsteroidal anti-inflammatory drugs, and coxibs with the catalytic and allosteric subunits of cyclooxygenases-1 and -2. J Biol Chem.

2019;294(5):1697-1705.

82. Ray S, Salzer I, Kronschläger MT, Boehm S. The paracetamol metabolite N-acetylp-benzoquinone imine reduces excitability in first- and second-order neurons of the pain pathway through actions on KV7 channels. Pain. 2019;160(4):954-964.

83. Pal N, Mandal S, Shiva K, Kumar B. Pharmacognostical, Phytochemical and Pharmacological Evaluation of Mallotus philippensis. Journal of Drug Delivery and Therapeutics. 2022 Sep 20;12(5):175-81.

84. Singh A, Mandal S. Ajwain (Trachyspermum ammi Linn): A review on Tremendous Herbal Plant with Various Pharmacological Activity. International Journal of Recent Advances in Multidisciplinary Topics. 2021 Jun 9;2(6):36-8.

85. Mandal S, Jaiswal V, Sagar MK, Kumar S. Formulation and evaluation of carica papaya nanoemulsion for treatment of dengue and thrombocytopenia. Plant Arch. 2021;21:1345-54.

86. Mandal S, Shiva K, Kumar KP, Goel S, Patel RK, Sharma S, Chaudhary R, Bhati A, Pal N, Dixit AK. Ocular drug delivery system (ODDS): Exploration the challenges and approaches to improve ODDS. Journal of Pharmaceutical and Biological Sciences. 2021 Jul 1;9(2):88-94.

87. Ali SA, Pathak D, Mandal S. A REVIEW OF CURRENT KNOWLEDGE ON AIRBORNE TRANSMISSION OF COVID-19 AND THEIR RELATIONSHIP WITH ENVIRONMENT. International Journal of Pharma Professional's Research (IJPPR). 2023;14(1):1-5.

88. Shiva K, Mandal S, Kumar S. Formulation and evaluation of topical antifungal gel of fluconazole using aloe vera gel. Int J Sci Res Develop. 2021;1:187-93.

89. Vishvakarma P, Mandal S, Verma A. A REVIEW ON CURRENT ASPECTS OF NUTRACEUTICALS AND DIETARY SUPPLEMENTS. International Journal of Pharma Professional's Research (IJPPR). 2023;14(1):78-91.

90. Ali S, Farooqui NA, Ahmad S, Salman M, Mandal S. CATHARANTHUS ROSEUS (SADABAHAR): A BRIEF STUDY ON MEDICINAL PLANT HAVING DIFFERENT PHARMACOLOGICAL ACTIVITIES. Plant Archives. 2021;21(2):556-9.

91. MANDAL S, JAISWAL DV, SHIVA K. A review on marketed Carica papaya leaf extract (CPLE) supplements for the treatment of dengue fever with

thrombocytopenia and its drawback. International Journal of Pharmaceutical Research. 2020 Jul;12(3).

92. Mandal S, Vishvakarma P, Verma M, Alam MS, Agrawal A, Mishra A. Solanum Nigrum Linn: An Analysis Of The Medicinal Properties Of The Plant. Journal of Pharmaceutical Negative Results. 2023 Jan 1:1595-600.

93. Vishvakarma P, Mandal S, Pandey J, Bhatt AK, Banerjee VB, Gupta JK. An Analysis Of The Most Recent Trends In Flavoring Herbal Medicines In Today's Market. Journal of Pharmaceutical Negative Results. 2022 Dec 31:9189-98.