CHAPTER 4
DISCUSSION AND CONCLUSION

In the present day, the use of medicinal plants and formulations derived from them as dietary supplements, nutraceutical functional foods and herbal medicinal products has become more widely accepted in Thailand. Therefore, it is important to evaluate the pharmacological activities and adverse effects of these plants and their preparations. *P. emblica* is one of the most commonly used herb in Thai traditional medicine. Generally, the ripened fruits have been consumed directly or commonly as a juice. According to Thai Herbal Pharmacopoeia (THP), the fruit of *P. emblica* is categorized in a group of expectorant, laxative with secondary astringent and antiscorbutic agent and it is recommended for a usage at 6-12 g/day (Department of Medical Sciences, Ministry of Public Health, 2000). Moreover, *P. emblica* has received high attention because decoction of their fresh and dried fruits are used in traditional medicine for the treatment of several illnesses such as diarrhea, jaundice and inflammatory disorders (Deokar, 1998; Khan, 2009). The present work was carried out to assess the anti-inflammatory, analgesic, antipyretic, chondroprotective, anti-ulcerogenic activities and toxicity of the standardized water extract from the fruit of *P. emblica* prepared according to THP. Because of their potential pharmacological activities, the toxicity data of *P. emblica* water extract should be obtained in order to validate its benefit and safety prior to the development of pharmaceutical products. Inflammation is one of the most important health problems, which has been linked to many acute and chronic diseases. At the present time, inflammatory diseases are also contributing to the increased worldwide morbidity and mortality rates (Crimmins and Finch, 2006). NSAIDs are the most widely used agents for inflammatory diseases. They act by inhibiting the synthesis and/or release of mediators and cellular events closely linked to the inflammatory responses. Although, NSAIDs are effective but their long-term use is limited by their side effects such as gastrointestinal toxicity, water and salt retention, and bone marrow depression. The adverse effects of NSAIDs lead to the development of new drugs, especially the selective inhibitors of

the inducible COX-2, which its induction occurs during inflammation, has been used to directly target in remodeling inflammation. Nowadays, the selective COX-2 inhibitors (e.g., celecoxib and etoricoxib, etc) has been developed and approved for inflammatory diseases in order to minimize adverse effects of the traditional NSAIDs (Katzung and Julius, 2004). However, both COX-2 inhibitor and NSAIDs are associated with a similar cardiovascular risk (Hinz *et al*., 2007).

The anti-inflammatory study of the standardized water extract of *P. emblica* was evaluated by using EPP- or AA-induced ear edema formation, carrageenan-induced paw edema as well as cotton pellet-induced granuloma models. Edema is a useful parameter for testing active agents in treating acute inflammation (Sedgwick and Willoughby, 1989). EPP or AA causes instant irritation of the mouse ear, which leads to fluid accumulation and edema characteristic of the acute inflammatory response. Suppression of this response indicates anti-inflammatory effect (Atta and Alkofahi, 1998).

The inflammatory mediators released in EPP-induced ear edema model are histamine, serotonin, bradykinin and PGs and these mediators are capable to promote vasodilatation and increase vascular permeability as well as synergistically producing edema (Brattsand *et al*., 1982; Carlson *et al.*, 1985). The reference anti-inflammatory drug, phenylbutazone acting by inhibition of COX enzymes, showed marked inhibitory effect on edema formation in this model. Similarly, the water extract of *P. emblica* exhibited inhibitory effect on ear edema formation at all assessment times. The results obtained suggest that *P. emblica* water extract possesses an anti-inflammatory activity in acute phase of inflammation via inhibition of release and/or formation of inflammatory mediators involved in edema formation.

The AA-induced ear edema is another skin model of inflammation which is useful for screening compounds showing inhibitory effect on the acute inflammatory reaction and is widely used to evaluate the anti-inflammatory activity of LOX inhibitors (Young *et al*., 1984; Opas *et al*., 1985). Topical application of AA to murine ears causes an increase of ear thickness, as well as an increase in LTB_4, LTC_4, and PGE_2 contents in the ear tissue (Horizoe *et al*., 1998). These mediators, especially LOX metabolites, are capable of promoting vasodilatation and increasing vascular permeability and may act synergistically to produce edema whereas COX

inhibitors have low or no activity (Chang *et al*., 1986; Di Martino *et al*., 1987). Phenidone, a dual inhibitor of 5-LOX and COX, could suppress AA-induced ear edema model. Its anti-edematous effect is mediated through the inhibition of LTC_4 biosynthesis but not through the inhibition of PGE_2 biosynthesis (Ishii *et al*., 1994). Furthermore, it has been reported that COX inhibitors such as phenylbutazone, ibuprofen and aspirin could markedly reduce the ear edema induced by EPP but not the edema induced by AA (Young *et al*., 1984; Griswold *et al*., 1987).

Results obtained from the AA-induced ear edema in rats in the present study showed that phenidone exhibited pronounce inhibitory effect whereas phenylbutazone and the water extract of *P. emblica* showed no inhibitory effect. *P. emblica* water extract exerted an inhibitory effect on the ear edema formation induced by EPP, but not on the AA-induced ear edema, this result indicates that the anti-inflammatory activity of the water extract of *P. emblica* does not involve the LOX pathway.

Carrageenan-induced hind paw edema is useful to detect active anti-inflammatory agents and has frequently been used to assess the anti-edematous effect of natural products. Several inflammatory mediators, e.g., histamine, serotonin, kinins, PGs, complement, and pro-inflammatory cytokines play a major role in paw edema caused by carrageenan (Di Rosa *et al*., 1971; Hirschelmann and Bekemeier, 1981). The initial phase is caused by the release of histamine and serotonin followed by the release of bradykinin during 1-2 h after carrageenan injection (Crunkhorn and Meacock, 1971). The release of PGs is closely associated with leukocytes migration to the inflammed site. The presence of PGs, particularly PGE_2, in the inflammatory exudates from the injected foot can be demonstrated at 3 h and thereafter (Di Rosa and Sorrentino, 1968). It is well established that the second phase is sensitive to most clinically effective anti-inflammatory drugs such as NSAIDs (Vinegar *et al*., 1969).

In the present study, aspirin reduced the paw edema after the carrageenan injection. Oral administration of *P. emblica* water extract showed a significant inhibition of carrageenan-induced hind paw edema. Base on the inhibitory effect of the *P. emblica* water extract seen at the 3rd h and 5th h, it suggests that the main mechanism of action may be due to inhibition of PGs synthesis. Moreover, the inhibitory effect of the *P. emblica* water extract may partly involve other acute inflammatory mediators such as histamine, serotonin, bradykinin and

pro-inflammatory cytokines which are released during the 1st h after carrageenan injection.

Cotton pellet-induced granuloma formation is commonly used as an in vivo test for chronic inflammation. The response to a subcutaneously implanted cotton pellet has been reported to involve a host inflammatory responses (Remes and Williams, 1992; Tang and Eaton, 1995; Hu *et al*., 2001), which can be divided into at least three phases, transudative, exudative and proliferative phases (Swingle and Shideman, 1972). Anti-inflammatory drugs can inhibit these responses by several mechanisms including inhibition of vascular permeability around the cotton pellet implantation, and interference with proliferative component of inflammatory process. However, NSAIDs such as aspirin has been found to elicit only a slight inhibition whereas steroidal anti-inflammation drugs have a strong inhibition on both transudative and proliferative phases of inflammation (Swingle and Shideman, 1972). Steroids such as prednisolone can prevent or suppress inflammatory reactions. However, long term treatment of steroids may induce the loss of body weight gain and thymus weight. These steroid effects may be due to peripheral catabolism of lymphoid and connective tissues, muscle, fat and skin (Schimmer and Parker, 2006). In chronic inflammation, the phagocytosis process is also believed to contribute to tissue damage by releasing large number of substances including lysosomal enzymes (e.g., phospholipase enzymes) and oxygen radicals (Tapper, 1996). Steroids can stabilize lysosomes thereby reducing the local release of proteolytic enzymes, hyaluronidase, and other substances that contribute to tissue swelling (Berne and Levy, 2004).

In the present study, *P. emblica* water extract and aspirin did not produce any inhibitory effect on both body weight gain and thymus weight whereas prednisolone markedly reduced both parameters. Moreover, prednisolone could normalize serum alkaline phosphatase activity by stabilizing the lysosomal membrane, whereas *P. emblica* water extract and aspirin did not affect this enzyme. The obtained results indicate that *P. emblica* water extract does not share steroidal-like activity.

Inflammatory reaction produces the synthesis and release of the inflammatory mediators, such as histamine, bradykinin, PGs, IL-1 and TNF-α, which their effects are related to pain and fever (Engblom *et al*., 2002; Ivanov and Romanovsky, 2004).

Therefore, analgesic and antipyretic activities of *P. emblica* water extract were pursued. The analgesic study of the *P. emblica* water extract was evaluated by using formalin test in mice. Formalin test is a very useful method not only for assessing antinociceptives, but also for elucidating the mechanism of analgesia, whether the site of action is central and/or peripheral (Shibata *et al*., 1989). This test consists of two distinct phases, possibly reflecting different types of pain (Dubuisson and Dennis, 1977; Hunskaar *et al*., 1985; Hunskaar and Hole, 1987; Tjolsen *et al*., 1992). The early phase starts immediately after an injection of formalin and lasts for 3-5 min. It is probably due to direct chemical stimulation of nociceptors (Dubuisson and Dennis, 1977; Hunskaar *et al*., 1985; Tjolsen *et al*., 1992). This phase can be inhibited by centrally acting antinociceptives (Hunskaar *et al*., 1985; Hunskaar and Hole, 1987). The late phase starts approximately 15-20 min after the formalin injection and lasts for 20-40 min. This phase seems to be due to the combination of an inflammatory response in the peripheral tissue, partly mediated by PGs (Tjolsen *et al*., 1992). This phase can be inhibited by NSAIDs (aspirin, indomethacin and naproxen) and steroids (dexamethasone and hydrocortisone), as well as the centrally acting drugs (Hunskaar and Hole, 1987).

In this study, morphine, aspirin and *P. emblica* water extract exhibited analgesic activity on both phases of the formalin test, but all drugs exerted more marked effect on the late phase. These results suggest that the principal mechanism of analgesic effects of *P. emblica* water extract may be due to the inhibition of the synthesis and/or release of inflammatory pain mediators such as PGs and other mediators at peripheral nociception sites. Moreover, the analgesic activity of *P. emblica* water extract may be partly centrally acting as well.

The body temperature is dependent on maintaining a balance between the production and dissipation of heat. Fever may be provoked by many exogenous substances in animal models including bacteria and their endotoxins, viruses, yeasts, protozoa, immune reactions, several hormones and medications. High body temperature involves the production of pro-inflammatory cytokines such as IL-1β, IL-6, IFN-α and TNF-α, which enter the hypothalamic circulation and stimulate the release of local PGs, resetting the hypothalamic thermal setpoint (Dalal and Zhukovsky, 2006). The antipyretic effect is commonly mentioned as one of the

characteristics of aspirin and some NSAIDs resulted from their inhibitory effect on the biosynthesis and/or the release of PGE_2 into the preoptic area of the anterior hypothalamus caused by endogenous pyrogens (Li *et al*., 2001; Dalal and Zhukovsky, 2006). In the present study, *P. emblica* water extract showed antipyretic activity by the decreasing body temperature of hyperthermic rats induced by brewer's yeast at all assessment times. The antipyretic activity of *P. emblica* water extract may be due to the inhibition of the synthesis and/or release of local PGE_2 into the hypothalamus.

Putting together, the anti-inflammatory, analgesic and antipyretic activities of the standardized water extract from the fruit of *P. emblica* prepared according to the THP seem to be similar to those of NSAIDs. Inhibitory effect on the synthesis and/or release of inflammatory or pain mediators (especially the products derived via COX pathway) may be the main mechanisms of action of *P. emblica* water extract. Therefore, its inhibitory effect on COX enzymes was evaluated by using COX inhibitor assay kit. In the present study, *P. emblica* water extract had an IC_{50} ratio of COX-1/COX-2 of 1.56 indicating that the extract acts as a non-selective COX inhibitor.

Inflammation is associated with osteoarthritis (OA), rheumatoid arthritis (RA) and other types of inflammatory arthritis. Moreover, aging and the proteolytic degradation of ECM macromolecules in articular cartilage in the joint are important catabolic events in OA and RA (Abramson and Attur, 2009; Goldring and Marcu, 2009; Loeser, 2009). Inflammation can occur around an affected joint. It is thought that the inflammation is caused by cartilage fragments that break off and irritate the synovium (the smooth lining of a joint). In OA, synoviocytes and synovial macrophages produce a wide array of inflammatory mediators including PGs, reactive oxygen species and pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. The stimulation of cartilage explants with IL-1β has shown the wide spread matrix degradation including loss of tissue proteoglycan and collagens. The mechanism of IL-1β induced ECM degradation involves the release of matrix metalloproteinase (MMP) and other degradative products which contribute to the chronic sequel leading to bone and cartilage destruction.

Chondroprotective agents are compounds that: 1) stimulate chondrocyte synthesis of collagen and proteoglycans, as well as synoviocyte production of

hyaluronan; 2) inhibit cartilage degradation; and 3) prevent fibrin formation in the subchondral and synovial vasculature (Ghosh *et al*., 1992). In this study, IL-1β increased the S-GAG and HA releasing into the culture medium. Moreover, IL-1β decreased the uronic acid and collagen content of the cartilage. *P. emblica* water extract significantly decreased HA level and trend to decrease S-GAG level in culture medium. Moreover, the extract trend to increase the uronic acid and collagen contents in cartilage tissue. Diacerein, which is generally used for the treatment of osteoarthritis, showed similar results to those of *P. emblica* water extract which lends support that the extract may possess chondroprotective activity. From previous study, *P. emblica* water extract contains gallic acid (polyphenolic compounds) about 20.48%. It has been reported that the polyphenol epigallocatechin-3-gallate in green tea exerts chemopreventive effect with a potential to inhibit the development of OA and RA (Singh *et al*., 2010). Further study for the chondroprotective effect of *P. emblica* water extract is warranted to confirm its use in OA or RA.

NSAIDs are widely used in the treatment of inflammatory diseases. Among their side effects are nausea, vomiting, diarrhea, constipation, decreased appetite, rash, dizziness, headache, and drowsiness. Moreover, NSAIDs may also cause fluid retention, leading to edema. The most serious side effects are kidney failure, liver failure, ulcers and prolonged bleeding after an injury or surgery. Moreover, many selective COX-2 inhibitors (e.g., celecoxib and meloxicam) are claimed to possess equal efficacy as non-selective COX inhibitors, but lesser adverse effects on the gut and the kidneys (Waller *et al*., 2005a), anyhow, their side effect on cardiovascular system has been reported (Hermann and Ruschitzka, 2007; Hinz *et al*., 2007).

In the present study, *P. emblica* water extract elicited the inhibitory effect on both COX-1 and COX-2 enzymes. Thus, the gastric ulcer may be one of the potential side effect of *P. emblica* water extract caused by its inhibitory effect on COX-1 enzyme. Anyhow, the water extract of *P. emblica* contains many kinds of substances. So far, there is no report concerning ulcerogenic effect of *P. emblica*. As many of anti-inflammatory plants exhibit anti-ulcerogenic effect (mentioned in introduction part), therefore, the three ulcerogenic models were used to evaluation of the anti-ulcerogenic activity of *P. emblica*.

The EtOH/HCl ulcer model is commonly employed for determining whether the anti-gastric ulcer activity involves the effects on gastric mucosal protective factors. EtOH/HCl-induced gastric lesions is due to a direct necrotizing effect to gastric mucosa (Miller and Henagan, 1984). Acid anti-secretory agents such as H_2-receptor antagonists (cimetidine) can prevent the gastric lesions induced by EtOH/HCl, and it is suggested that the activity is attributable to cytoprotective activity and partly to their ability to suppress acid secretion (Miyata *et al*., 1991).

Indomethacin, a non-selective COX inhibitors, causes gastric and intestinal ulceration, reduction of gastric mucosal blood flow and delay of gastric healing (Robert, 1979). Lipid peroxidation (Yoshikawa *et al*., 1993) and oxygen radicals (Naito *et al*., 1993), including the superoxide radical, play an important role in the microvascular injury induced by indomethacin, which in turn plays a primary role in the development of gross hemorrhagic erosions. Moreover, it has been reported that the erosions induced by indomethacin are prevented by acid anti-secretory agents such as proton pump inhibitors (Fukui *et al*., 1988), H_2-receptor antagonists (Kuratani *et al*., 1992) and antioxidant enzymes (Naito *et al*., 1993).

The water immersion and hypothermic restraint stress are widely used as experimental models to induce acute stress ulcers in rats (Takagi and Okabe, 1968; Grossman, 1981). The increase of gastric acid secretion (often termed as the "aggressive factor") is considered to be an important factor in genesis of stress ulcer (Goa and Monk, 1987) and vagal overactivity (Dai and Ogle, 1975) has been suggested as the principle effector in stress-induced ulceration. Vagotomy has tropic effects on the gastric mucosa, acid secretion and is protective against stress (Landa García *et al*., 2002). Moreover, the gastric lesions induced by stress could be prevented by anti-secretory agents such as H_2-receptor antagonists, anti-cholinergic agents and proton pump inhibitors (Yoshida *et al*., 1999).

In the present study, the oral administration of the water extract of *P. emblica* did not produce gastric lesions. On the contrary, the extract reduced ulcer formation in all tested acute gastric ulcer models i.e. EtOH/HCl-, indomethacin-, and stress-induced gastric lesions. These results indicate that *P. emblica* water extract possess anti-ulcerogenic effect. The standardized water extract of *P. emblica* fruits is a crude extract that composes many chemical compounds such as flavonoids, hydrolysable

tannin, saponin, and terpenes. From the phytochemical study, the water extract of *P. emblica* contained tannins about 42.51%. Moreover, the HPLC analysis of water extract of *P. emblica* showed the presence of 20.48% gallic acid. From the previous studies, tannin, a astringent agent, has been reported to possess gastroprotective and anti-ulcerogenic effects (Ramirez and Roa, 2003). Meanwhile, gallic acid possesses a potent antioxidant activity (Naito *et al*., 1993) and has the ability to heal indomethacin-induced gastric mucosal damage by modulating inflammatory response (Bhattacharya *et al*., 2007) and prevents NSAID-induced gastropathy by blocking oxidative stress (Pal *et al*., 2010). Thus, gallic acid as well as tannin might be the main constituents responsible for anti-ulcerogenic effect of the *P. emblica* extract.

For assessment and evaluation of the toxic characteristics of the *P. emblica* water extract, acute oral toxicity and chronic oral toxicity tests in rodents are usually performed. In acute oral toxicity study, a single oral administration of *P. emblica* water extract at the dose of 5,000 mg/kg body weight was given to both sexes of rats. The extract neither significantly changed the body weight nor internal organ weight of treated male and female rat relative to those of the control group. Furthermore, neither changes in animal behaviors nor toxic signs were detected in treated rats. The results revealed no gross and pathological abnormality after an acute exposure. This is an indication that the extract has low acute toxicity after oral administration. According to OECD guideline (2001), the lower limit of dose of test substance for acute oral toxicity is 2000 or exceptionally 5,000 mg/kg. The obtained result from acute toxicity study indicates that the *P. emblica* water extract is fairly non-toxic.

For evaluation of chronic toxicity, the animal dosage of crude plant material for rats can be calculated according to Reagan-Shaw *et al*. (2008). The doses of 300, 600 and 1,200 mg/kg/day crude *P. emblica* water extract equivalent to 2.8-22.2 times of the normal human dose (crude plant material, 100-200 mg/kg/day) (Appendix C) were set for the experimentation. In this study, the body weight gain on the 270th day of both female and male treated rats showed a significant decrease from that of the control group. However, the result from monitoring animal health in the entire period of 270 days showed no sign of morbidity and diseases. Furthermore, both female and male rats were healthy as shown by the normal appearance of general behaviors, respiratory pattern, cardiovascular signs, motor activities, reflexes, and normal change

in skin and fur. Although the body weight and body weight gain of extract-treated rats were significantly different from those of the control animals, but these differences were very small and within normal limit. Moreover, food intake of all groups was not significantly altered. Therefore, the changes of body weight and body weight gain in extract-treated group may not be of clinical significance.

The hematopoietic system is very sensitive to toxic compounds and can be altered by the ingestion of some toxic plants (Adeneye *et al*., 2006). The parameters usually measured are hemoglobin, packed cell volume, white blood cell count, platelets count. Hematological parameters provide vital information regarding the status of bone marrow activity and intravascular effects such as hemolysis and anemia (Gregg, 2000). The morphological examination of red blood cells and white blood cells indicate their production or destruction. Moreover, white blood cell count (basophil, eosinophil, lymphocyte, monocyte, and neutrophil) is also performed in order to evaluate immune system (Williams *et al*., 1990; Gregg, 2000; Levine, 2002).

In this study, some of the hematological and differential white blood cell count values (such as mean corpuscular hemoglobin concentration, platelet, neutrophil and lymphocyte) of treated rats were significantly different from those of the control group. Nevertheless, all values lied within the normal limits the results are considered as normal for this animal species (Feldman *et al*., 2000; Inala *et al*., 2002). Therefore, these results suggest that the water extract of *P. emblica* did not cause hematological or immunological defects.

Clinical blood chemistry examination was performed in order to evaluate any toxic effects on the pancreas function (glucose), kidney function (BUN, creatinine) and liver function (SGOT, SGPT, ALP, total protein, albumin, total and direct bilirubin). With regard to the metabolic effect, plasma glucose is monitored to demonstrate the effect of drug on glucose metabolism. For evaluation of kidney function, acute or chronic renal failure is the most common cause of elevated BUN and increased creatinine. Liver function testing is a blood test used to evaluate various functions of the liver, as metabolism, storage, filtration, and excretion. Conditions commonly associated with abnormalities of liver function testing include gallbladder disease, hepatitis, fatty liver, cirrhosis, infectious mononucleosis and alcoholism (Young and Holland, 1995; Levine, 2002).

In this study, significant decreases and increases in clinical blood chemical values were observed in both female and male rats as compared to the control groups. However, the alteration of these values was minor and remained within the normal range (Caisey and King, 1980; Sacher and McPherson, 2000; Angkhasirisap *et al*., 2002; Levine, 2002). These data suggest that *P. emblica* water extract does not induce toxicity to the pancreas, kidneys, and liver.

Necropsy and histopathological examinations are performed to further confirm whether the internal organs or tissues had been damaged. The organs of interests are brain, lungs, heart, liver, kidneys, pancreas, spleen, stomach, duodenum, small intestine, and sex organs. The general appearances and the internal organs of rats receiving the extract showed normal structure, size, weight, shape, color, and texture. The increase or decrease of the internal organ weight obtained in the present study was statistically significant. Minimal congestion of the internal organs, especially the lungs, liver, and kidneys was founded. However, these changes could be due to the biological variation of the animals (Auletta, 2002; Bailey *et al*., 2004) and seem not to be associated with the toxic effect of the *P. emblica* water extract. Nevertheless, significant change in both vital organs and other internal organs were not found. The testes and the ovaries were well preserved with intact spermatogenesis and formation of corpora to suggest that the extract did not affect reproductive cycles of the animals. All of these results indicate that *P. emblica* water extract is relatively safe.

In conclusion, the anti-inflammatory effect of *P. emblica* water extract was evidenced by the significant reduction of acute inflammatory reaction as proved by ear edema formation induced by EPP application and by inhibition of carrageenan-induced rat hind paw edema. Nevertheless, *P. emblica* water extract did not have inhibitory effect on AA-induced ear edema in rats. The results indicate that the anti-inflammatory effect of *P. emblica* water extract probably mediates via inhibition of COX pathway but not the LOX pathway. *P. emblica* water extract did not reduce transudative and proliferative phases, body weight gain and thymus weight in cotton pellet-induced granuloma formation. Therefore, this finding suggests that anti-inflammatory activity of *P. emblica* water extract is free of steroidal-like action. The extract elicited significant analgesic activity in a dose-dependent manner on both the early and late phase of formalin test, but it exerted more marked effect in the late

phase. The analgesic activity of *P. emblica* water extract may be via both peripheral acting and partly centrally acting. Antipyretic study showed that *P. emblica* water extract possessed significant reduction of rectal temperature probably due to its inhibition of PG synthesis/release in hypothalamus. Moreover, *P. emblica* water extract inhibited both COX-1 and COX-2 enzymes. The main mechanism of anti-inflammatory, analgesic and antipyretic activities of the standardized water extract of *P. emblica* seems to act via the inhibition of the synthesis and/or release of inflammatory or pain mediators, especially PGs. Besides, *P. emblica* water extract decrease HA level in the medium, it seems to possess chondroprotective activity. Anti-ulcerogenic activity of *P. emblica* water extract was profound as shown by the significant reduction on three gastric lesion models in rats (EtOH/HCl, indomethacin, and stress). It is likely that *P. emblica* water extract possesses the gastroprotective activity. In addition, *P. emblica* water extract did not produce any toxic signs and symptoms of acute (5,000 mg/kg) and chronic oral toxicity tests. It can be concluded that the anti-inflammatory, analgesic and antipyretic activities of the extract are mediated through inhibition of COX isoenzymes. It also possesses gastroprotective and chondroprotective effects. The obtained results from toxicity study indicate that it is relatively non-toxic.