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RESEARCH ARTICLE

Ameliorative Effect of Bradykinin Potentiating Factor on Haematological and Biochemical Changes Induced by Indomethacin in model ulcer animals.

Abu-Amra, E.; **Abd-EL-Rehim, S. A.; Lashein, F.M.; Seleem, A. A.; Shoaeb, H. S. I.**
Zool. Dept., Fac. Sci., Sohag University, Egypt

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Corresponding Author

Abu-Amra, E

Abstract

Many biologists tried different means of treatment the deleterious effects of indomethacin either by natural products or biological substances. Accordingly, the present study aims to investigate the protective effect of BPF_7 as a natural products separated from the venom of jellyfish, *Cassiopia andromeda* on indomethacin induced some haematological and biochemical changes in model ulcer animals. The results showed that, the oral administration of indomethacin (10mg/kg b.w) daily induced leukopenia, lymphopenia and monocytopenia, but the animals treated orally with indomethacin (10mg/kg b.w) day after the other induced leukocytosis, lymphocytosis and monocytosis. In addition, the indomethacin daily or day after the other induced a significant decrease in RBCs count, haematocrit value (HCT) and haemoglobin (Hb) compared to control group. On the contrary, the animals and the ulceration groups treated with BPF_7 did not induce any significant changes in all previous haematological parameters except lymphocytes and monocytes. Also, the results indicated that antioxidant enzymes (GST and CAT) and nitric oxide (NO) contents in liver, kidney and stomach homogenates were inhibited by indomethacin and the BPF_7 improved these enzymes and nitric oxide to near control group level. The abnormalities induced by indomethacin in these haematological and biochemical parameters may be related to impaired the bone marrow, liver, kidney and stomach or may be to gastrointestinal bleeding, inhibits erythropoiesis, reduction in the cellular antioxidant enzymes and endothelial NO synthesis in tested tissues. On the other hand, these results indicated that the BPF_7 significantly ameliorated the toxic effects exerted by indomethacin. This improvement may be attributed to potentiate the endogenous bradykinin by this factor, stimulate the release of prolactin, proliferation of the bone marrow, lymphopoietic cells and enhanced lymphoid organs.

INTRODUCTION

The non-steroidal anti-inflammatory drugs (NSAIDs) are chemically heterogeneous compounds that have therapeutic and toxic effects in common (Higgs, 1984). The effect of indomethacin on haematological and biochemical changes in blood have been carried out by several investigators (Adedapo and Aiyelotan, 2001; Abatan *et al*., 2006; Silva *et al*., 2012). Indomethacin is a very effective NSAID but its use is limited by a high incidence of adverse reactions including blood disorders, leukopenia, lymphopenia, monocytopenia bleeding together with aplastic anaemia resulting from blood loss (Cuthbert, 1974; Robert, 1981; Whittle and Vane, 1983; Gilman *et al.*, 1985).

Recently, reactive oxygen species (ROS) have shown to play a critical role in the gastric ulceration (Das *et al*., 1997). Reactive oxygen species such as superoxide radical (O_2), hydrogen peroxide (H_2O_2) and hydroxyl

radicals (OH^-) damage membrane proteins by causing lipid peroxidation in membranes by attacking unsaturated fatty acids (Ames *et al*., 1993; Kato *et al*., 1997). The antioxidant defense including antioxidant enzymes, foods and drugs are important in the prevention of oxygen-derived free radicals (toxic effects) which cause many diseases. Moreover, the activities of anti-oxidative enzyme are used as markers for ulceration processing following oral administration of indomethacin- induced ulcers (Mates *et al*., 1999; Dengiz *et al*., 2007). Catalase, glutathione s-transferase and glutathione reductase are part of the enzymatic defense mechanisms against the toxicity and tissue damage of reactive oxygen species (ROS) (Bradley *et al*., 1982).

Some studies have shown that indomethacin performs pro-oxidant activity, initiates lipid peroxidation and decrease glutathione peroxidase activity by generating ROS (Yoshikawa *et al*., 1993; Naito *et al*., 1998). The pro-oxidants block mucosal cells antioxidant systems which cause reactive oxygen species (ROS) formation that lead to oxidative damage (Figge and Figge, 1990; Elliot and Wallace, 1998).Indomethacin is known to induce the reactive oxygen metabolites in animal models which may contribute to mucosal injury (Chattopadhyay *et al*., 2006). These free radicals also damage the cellular antioxidant enzymes which acting as the first line of cellular defense against oxidative injury. This might lead to aggravated tissue damage during stomach ulceration (El-Missiry *et al*., 2001).

Reactive oxygen species (ROS) are highly cytotoxic and thus act as apoptotic factors (Garrel *et al*., 2007). Antioxidant enzymescontrol the ROS concentration and keep the balance between ROS generation and ROS elimination which help in maintaining cellular functions. An increase in intracellular ROS levels or a decrease in antioxidant enzyme levels can lead to apoptosis and cell death (Juengel *et al*., 1993;Buttke and Sandstorm, 1994; Garrel *et al*., 2007). Several endogenous mediators including vascular leukocytes, mast cells, reactive oxygen metabolites and nitric oxide (NO) have been implicated as the modulators of epithelial barrier integrity under physiological and patho-physiological states (Horton andWalker, 1993; Kubes, 1993; Kanwar *et al*., 1994). Moreover, the key factor in modulating microcirculation is nitric oxide (NO). When the mucosa is exposed to an irritant, a rapid increase in mucosal flow occurs. This response is initiated by sensory nerves underlying the epithelium and its stimulation results in activation of endothelial nitric oxide synthase (e-NOs) and subsequent production of nitric oxide (Hsu and Liu, 2004).

Nitric oxide has also been shown to have protective effects in some experimental ulcer models (Gürbüz *et al*., 1999). Similarly, Ma and Wallace (2000) found that the endothelial nitric oxide synthase plays a significant role in gastric ulcer healing. Several studies have reported that administration of nitric oxide donors protect the gastrointestinal mucosa against damage induced by indomethacin (Gürbüz *et al*., 1999; Khattab *et al*., 2001; Dengiz *et al*., 2007).

It is interesting to note that the sea animals are a source of a large group of structurally unique natural products that are mainly found in invertebrates such as sponges, tunicates, mollusks and coelenterates (Allonso *et al*., 2003). Coelenterates are aquatic invertebrates responsible for more envenomation than any other marine phyla. The majority of the toxins of coelenterates contain a complex mixture of polypeptides and proteins including catecholamine, histamine, serotonin, phospholipases, proteases and kinines (David, 2005;Jeffrey, 2005). Some venom and its extracts were found to be of medical importance (Rich and Cheras, 2009). Also, venoms extracts of anti-inflammatory and protective functions were reported by various authors (Mayer and Lehmann, 2000; Sankar*et al*., 2013). Bradykinin potentiating factors (BPFs) potentiate the effects of BK both in *vivo* and in *vitro* and have been reported to be found in the venom of some toxic animals shown to enhance protein enzyme biosynthesis, DNA and carbohydrates in liver tissue (Seleem, 2003) and protect the liver from the toxicity of patulin mycotoxin (Abd El-Rehim, 2009).Accordingly, the present study aims to investigate the protective effect of BPF_7 as a natural products separated from the venom of jellyfish, *Cassiopia andromeda* on indomethacin induced some haematological and biochemical changes in model ulcer animals

MATERIALS AND METHODS

Indomethacin

Indomethacin was obtained commercially from Khaira Pharm. Chem. IND. CO. Cairo, Egypt.

Bradykinin-potentiating factor (BPF_7)

Jellyfish, *Cassiopia andromeda*, is distributed in the Red Sea and it was reported as a venomous species. In this study, jelly fish, *Cassiopia andromeda*, was collected from two shallow water locations at 60 km and 70 km northern and southern of Quasar city, Egypt. Aqueous extracts were centrifuged. The supernatant was frozen.The BPF_7 separated from jelly fish was isolated and purified according to the method of Ferreria (1965).

Animals

60 healthy adult male albino mice (25 - 30g) from the breeding unit, department of Zoology, faculty of Science, Sohag University were used. The animals were housed under normal conditions in wire cages throughout the experimental period (15 days).

Experimental Procedure

Animal grouping

Animals were divided into six groups each composed of 10 animals. The first group served as a control group (G1). The mice of the second and the third groups (G2, G3) received repeated oral doses (10 mg/kg b.w.) daily or day after the other, respectively, during 15 days in order to induce ulcers (Davies, 1998; Abdel Galil and El-Awdan, 2012). The fourth group was injected intraperitonally (i.p.) daily with BPF_7(10µg/gm b.w) for 15 days. The fifth and sixth groups were also induced for gastric ulcer with commercial indomethacin orally as described previously in group two and group three, respectively, in addition these groups treated with BPF_7 as used in treating the fourth group .

Processing

At day 15, all animals of each group were sacrificed and dissected. The blood samples were taken from the heart in plastic tubes containing EDTA as anticoagulant used for the haematological studies.From each animal, liver, kidney and stomach were taken quickly. Parts of these organs were weighted and homogenized in phosphate buffer solution PH 7.4 using glass hand homogenizer and centrifuged at 3000 r.p.m. for 10 minutes. The supernatant was separated and stored at -20 C° until used for biochemical analysis.

Haematological and Biochemical analysis

Haematological investigations include white blood cell count (WBCs), lymphocytes count (Ly), monocytes count (Mon), granulocytes count (Gr), red blood corpuscles count (RBCs), haemoglobin content (Hb) and haematocrit value (HCT). These haematological parameters were measured using cell counter (HA-vet Automatic Hematology Analyser,Belgium; S/N HA3DM004). Glutathione s-transferase and catalase activity was determined for liver, kidney and stomach as described byHabig *et al*. (1974) and Aebi, H. (1984), respectively. Nitric oxide was determined according to Montgomery and Dymock (1961).

Statistical analysis:-

Results were expressed as mean ± S.E and statistically processed usingt-test for comparison between each experimental group and the control. Statistical significance was acceptable at a level of $P<0.05$.

Results and Discussion

The present study revealed that, the administration of indomethacin daily induced a significant decrease in WBCs count and its different cells, lymphocytes, monocytes and granulocytes. While the indomethacin day after the other alternative induced increase in these previous parameters in comparison with those of the normal control group. These results showed that, there was a significant dose dependent adverse effect of indomethacin in male mice (Tables 1, 2). The obtained results are not in agreement with Gilman *et al*. (1985). But our results are parallel with those obtained by many investigators (Adedapo and Aiyelotan, 2001; Bengtsson *et al*., 2006; Silva *et al*., 2012). It is suggested that the abnormalities induced by indomethacin in the leucocytes count and its different cells may be related to impaired leucocytes development in the bone marrow (Rabinovitz and Van Thiel, 1992; Strom *et al*., 1993), alterations in defense mechanism and /or due to inflammatory effect resulting from the indomethacin administration (Wolfe *et al*., 1999).On the other hand, the functions of leucocytes especially neutrophils in the blood are regulated by hormone like substances called leukotrienes (Nilsson *et al*., 1995; Harold and Ballard, 1997). Thus, the changes induced by indomethacin in the RBCs may be due to a direct action of drug which in turn reduced leukotriene production.

The results indicated that, the administration of normal animals with indomethacin daily or alternative also induced a significant decrease in RBCs count, hemoglobin (Hb) and hematocrit (HCT) values as compared to the control group (Tables 3 - 4). Similar results were observed by many investigators (Shridar and Narayanan, 2007; Basavraj *et al*., 2012). Indomethacin is associated with intestinal permeability, inflammation and bleeding (Davies, 1998; Wolfe *etal*., 1999). Therefore, these results may be attributed to lose of blood during gastrointestinal bleeding as a consequence of increased intestinal permeability especially at the sites of peptic ulcers causing decrease in these previous parameters (Wolfe *et al*., 1999; Adedapo and Aiyelotan, 2001). Another reason for panocytopenia after treatment the normal male mice with indomethacin is the impaired haematopoiesis owing to the injury of kidney, liver and bone marrow with the use of indomethacin which induce toxicity in these organs (Rabinovitz and Van Thiel, 1992; Strom *et al*., 1993). In addition, this effect may be related to inhibition of mitochondrial protein synthesis or DNA damage that occurs in the haemopoietic stem cells leading to a severe reduction in proliferation which in turn inhibits erythropoiesis (Strom *et al*., 1993; Basivireddy *et al*., 2002). Moreover, indomethacin inhibit the enzyme cyclooxygenase (cox) which catalyzes the conversion of arachidonic acid to prostaglandin (PGs) and thromboxane (Seibert *et al*., 1994) and it also inhibits cyclic adenosine monophosphate (cAMP) which has a regulatory role in the erythropoiesis leading to decrease in RBCs, Hb and HCT values (Robert, 1981). In addition, Gill *et al*. (1991) reported that changes in the haemoglobin level are almost parallel to the RBCs count.

In contrast, the results indicated that the normal animals treated with BPF_7 only and the ulceration groups treated with BPF_7 did not induce any significant effect in all hematological parameters except lymphocytes and

monocytes as compared to normal control animals whereas there were significant alterations in these parameters as compared with indomethacin groups (Tables 1 – 4).According to the results of the present study, there was a correlation between the RBCs, Hb and HCT. Also, BPF_7 treatment protects intestinal damage as well as improvement in haematological parameters. Therefore, the study suggests that this factor has the potential of ameliorating the toxic effects of indomethacin possibly by acting as an anti-inflammatory agent. In support of this, several compounds or natural products extracted from marine organisms were recognized to exert an activity against human pathologies (Jimeno*et al*., 2003; Proksch *et al*., 2003). Also,it has influenced on some diseases and to be anti-inflammatory, antiplatelet and antitumor as reported (Cragg and Newman, 1999; Mayer and Hamann, 2002; Mayer and Lehmann, 2001; Mayer *et al*., 2009).

Moreover, the bradykinin potentiating factor (BPF_7) separated from the venom of jelly fish, *Cassiopia andromeda* demonstrated that this factor contain 16 bioactive amino acids (Seleem, 2003).Accordingly, the improvement of the erythrocyte count accompanied with an improvement in the Hb and HCT may be related to the ability of this factor to potentiate the effects of bradykinin in mammalian cells. Because bradykinin (BK) is considered as an important mediator of the inflammatory response in many organs and it can activate the kinin B1 receptor (bradykinin receptor B1) which expressed only as a result of tissue injury. The B1 receptor plays an important role in chronic pain and inflammation (McLean *et al*., 2000). In addition, the vasoactive polypeptides such as BK and classical hormonal transmitters stimulate the synthesis or release of prolactin and growth hormones (Vijayan *et al*., 1979; Enjalbert *et al*., 1980; Frawley and Neil, 1981; Chihara *et al*., 1982; Samson *et al*., 1982) which in turn increase protein synthesis, stimulate the proliferation of mammalian cells (Montogomery *et al*., 1980) and differentiation of the bone marrow hematopoietic cells (Peng *et al*., 2006) leading to the erythrocyte formation and improvement. Furthermore, BK stimulates prostaglandin release and synthesis (El-Saadani, 2004; Levant *et al*., 2006) which may be promote the observed effects through the stimulation of kidney erythropoietin leading to enhanced erythropoiesis (Ganong, 1995) and consequently improving Hb and HCT values (Piron *et al*., 2001).The increase and improvement in the leucocytes and its different cells may be due to a direct effect of BPF_7 which stimulates and enhanced the lymphoid organs leading to an increase of lymphocytes count. Also, the BK enhances prostaglandins synthesis (Levant *et al*., 2006) which have a regulatory role in myelopoiesis (Kornberg and Rachmilewitz, 1982) leading to an increase and improvement in the granulocytes and monocytes counts as observed in the present study (Hoffbrand and Petti, 1993).

Glutathione s-transferase, Catalase and Nitric oxide activity

Compared with the normal control GST, CAT and NO contents were found to be significantly decreased in tissue of liver, kidney and stomach of animals administrated with indomethacin daily or alternative (Tables 5 – 10). These results are parallel with those obtained by many investigators (Lanas*et al*., 2000; Cardici*et al*., 2007; Dengiz *et al*., 2007;; El-Demerdash*et al*., 2010; Abdallah *et al*., 2011; El-Maddawy and El-Ashmawy, 2013).In addition, indomethacin induced the reactive oxygen metabolites in animal models which may contribute to mucosal injury (Chattopadhyay *et al*., 2006). These free radicals damage the cellular antioxidant enzymes such as GST and CAT which lead to aggravated tissues damage during stomach ulceration (El-Missry*et al*., 2001; El-Sheikh and El-Moselhy, 2014). Tripp and Tepperman (1995) reported a decrease in NO biosynthesis that was associated with an increase in the extent of damage. Therefore, these findings induced by indomethacin may be attributed to its direct local toxicity in tested tissues (Gürbüz *etal*., 1999) or due to the indomethacin- induces a reduction in endothelial NO synthase (eNOS) and subsequent reduction in endogenous tissues NO content in the studied organs (Slomiany *et al*., 1999).

On the other hand, the BPF_7 treated animals (G4) and the ulceration groups (G5 and G6) treated with BPF_7 showed a significant increase and improvement in GST, CAT and NO contents in liver, kidney and stomach homogenates compared to the model ulcer animals (G2 and G3), (Tables 5 – 10). The improvement of the previous parameter was attributed to the direct effect of this isolated factor and to the potentiation of endogenous bradykinin by BPF_7 which in turn stimulates the release and synthesis of prostaglandins (PGs) (Levant *et al*., 2006). These findings were agreewith the finding of Danielisova *et al*. (2008) who reported that bradykinin increased significantly some antioxidant enzymes such as catalase enzyme. Also, PGs enhancing the intracellular glutathione enzyme (GSH) concentration that potentiate cellular defense (Homem de BittencourtJr*et al*. 1998). In addition, Abd El-Hady *et al*. (2007) found that GSH acts as the first line of cellular defense against oxidative injury. Also, Ajaikumar*et al*. (2005) showed that, GSH prevent tissue damage by keeping ROS at low levels and at certain cellular concentration. In addition, increased NO level may be attributed to the activation of bradykinin receptor (B2R) leading to the formation of NO, a potent scavenger molecule which could reduce the accumulation of reactive oxygen species (ROS) (Allard *et al*. 2007) that play acritical role in the gastric ulceration (Dengiz *et al*., 2007; Danielisova *et al*., 2008).

Table (1): Effect of BPF_7on WBCs and lymphocytes count of male mice treated with indomethacin daily and day after the other for 15 days in different groups.

parameters		(G1) Control	(G2) INDO daily	(G3) INDO alternative	(G4) BPF_7	(G5) INDO+ BPF_7 daily	(G6) INDO+ BPF_7alternative
WBCsX 10^3/ uL	Mean ±SE	7.50±0.35	3.11±0.21	12.4±0.47	8.12±0.20	5.39±0.16	7.44±0.27
	Significance(1)		p<0.001	p<0.001	p>0.05	p>0.005	p>0.05
	Significance(2)			p<0.001	p<0.001	p<0.001	p<0.001
	Significance(3)				p<0.001	p<0.001	p< 0.001
	% of change (1)		-58.5	+65.3	+8.26	-28	-0.8
	% of change (2)			+298.7	+161.09	+73.3	+139.2
	% of change (3)				-34.5	-56.5	-40
Lymph X 10^3/ uL	Mean ± SE	3.80±0.25	2.50±0.124	7.48±0.38	5.6±0.144	4.55±0.33	5.93±0.158
	Significance(1)		P< 0.01	p< 0.001	p< 0.005	P<0.05	p< 0.001
	Significance(2)			p< 0.001	p< 0.001	p< 0.005	p< 0.001
	Significance(3)				p< 0.01	p< 0.005	p< 0.01
	% of change (1)		-34.2	+96.8	+47.36	+19.73	+56
	% of change (2)			+199.2	+124	+82	+137.2
	% of change (3)				-25	-39	-20.7

Non – significantp>0.05, significant p< 0.05, highly significant p<0.001
Significance (1): from G1. Significance (2): from G2. Significance (3): from G3.
%of change (1): different from G1. % of change (2): different from G2. % of change (3): different from G3.

Table (2): Effect of BPF_7 on Monocytes and Granulocytes count of male mice treated with indomethacin daily and day after the other for 15 days in different groups.

parameters		(G1) Control	(G2) INDO daily	(G3) INDO alternative	(G4) BPF_7	(G5) INDO+ BPF_7 daily	(G6) INDO+BPF_7 alternative
Mon X 10^3/ uL	Mean ±SE	0.89±0.092	0.23±0.04	1.2+0.085	1.76±0.197	0.52±0.04	0.73±0.079
	Significance(1)		p< 0.005	p<0.05	p<0.01	p< 0.05	P<0.05
	Significance(2)			p< 0.001	p<0.001	p< 0.005	p< 0.005
	Significance(3)				p<0.05	p< 0.001	p< 0.01
	% of change (1)		-74	+34.8	+97.7	-41.5	-17.9
	% of change (2)			+421.7	+665	+126	+217
	% of change (3)				+46.6	-56.6	-39.16
GR X 10^3/ uL	Mean ± SE	1.41±0.19	0.61±0.06	2.13±0.18	1.44±0.103	0.88±0.085	1.045±0.169
	Significance(1)		p< 0.05	p<0.05	p>0.05	P >0.05	p>0.05
	Significance(2)			p< 0.001	p< 0.001	p< 0.05	P < 0.05
	Significance(3)				p<0.05	p< 0.005	p<0.01
	% of change (1)		-56.7	+51.06	+2.1	-37.5	-25.8
	% of change (2)			+249	+136	+44.26	+71
	% of change (3)				-32.3	-58.6	-50.9

Non – significantp>0.05, significant p< 0.05, highly significant p<0.001

Significance (1): from G1. Significance (2): from G2. Significance (3): from G3.
%of change (1): different from G1. % of change (2): different from G2. % of change (3): different from G3.

Table (3): Effect of BPF_7on RBCs count and haemoglobin concentration of male mice treated with indomethacin daily and day after the other for 15 days in different groups.

parameters		(G1) Control	(G2) INDO daily	(G3) INDO alternative	(G4) BPF_7	(G5) INDO+ BPF_7 daily	(G6)INDO+ BPF_7alternative
RBCs X 10^6/ uL	Mean ±SE	7.9±0.39	4.15±0.36	5.1±0.67	7.4±0.59	7.3±0.51	8.38±0.28
	Significance(1)		p< 0.001	p< 0.05	p>0.05	p>0.05	p>0.05
	Significance(2)			p>0.05	p< 0.005	p< 0.005	p< 0.001
	Significance(3)				p< 0.05	p< 0.05	p< 0.01
	% of change (1)		-47.4	-35.4	-6.3	-7.59	+6.07
	% of change (2)			+22.8	+78.3	+75.9	+102
	% of change (3)				+45	+43	+64.3
Hb g/dL	Mean ±SE	12.20±0.64	5.8±0.46	6.2±0.8	12.8±0.52	9.65±0.99	15.5±1.34
	Significance(1)		p< 0.001	p< 0.005	P>0.05	P> 0.05	p>0.05
	Significance(2)			P>0.05	p<0.001	P<0.05	p<0.001
	Significance(3)				p< 0.001	p< 0.05	p< 0.005
	% of change (1)		-52	-49	+4.9	-20.9	+27
	% of change (2)			+6.89	+120.6	+66.3	+167
	% of change (3)				+106.45	+55.6	+150

Non - significant p>0.05, significant p< 0.05, highly significant p<0.001.
Significance (1): from G1. Significance (2): from G2. Significance (3): from G3.
%of change (1): different from G1. % of change (2): different from G2. % of change (3): different from G3.

Table (4): Effect of BPF_7on HCT% of male mice treated with indomethacin daily and day after the other for 15 days in different groups.

parameters		(G1) Control	(G2) INDO daily	(G3) INDO alternative	(G4) BPF_7	(G5) INDO+ BPF_7 daily	(G6) INDO+ BPF_7 alternative
HCT%	Mean ± SE	35.45±1.6	16.14±1.02	23.69±2.5	36.78±1.76	32.89±1.57	37.26±1.35
	Significance(1)		p<0.001	p<0.05	P>0.05	P>0.05	P>0.05
	Significance(2)			P<0.05	p< 0.001	p< 0.001	p< 0.001
	Significance(3)				p< 0.01	p< 0.05	p< 0.005
	% of change (1)		-54.4	-33.17	+3.75	-7.22	+5.1
	% of change (2)			+46.7	+127.8	+103.7	+130.8
	% of change (3)				+55.25	+38.8	+57.28

Non – significantp>0.05, significant p< 0.05, highly significant p<0.001.
Significance (1): from G1. Significance (2): from G2. Significance (3): from G3.
%of change (1): different from G1.% of change (2): different from G2.% of change (3): different from G3.

Table (5): Effect of BPF_7on glutathione s-transferase enzyme activity U/g in tissue of liver and kidney of male mice treated with indomethacin daily and day after the other for 15 days in different groups.

parameters		(G1) Control	(G2) INDO daily	(G3) INDO alternative	(G4) BPF_7	(G5) INDO+ BPF_7 daily	(G6) INDO+ BPF_7 alternative
Liver U/g	Mean ± SE	25±0.636	13.43±0.62	15.5±0.43	30.48±0.81	21.09±0.46	20.5±0.34
	Significance(1)		p< 0.001	p< 0.001	p< 0.005	p< 0.005	p< 0.005
	Significance(2)			p< 0.05	p< 0.001	p< 0.001	p< 0.001
	Significance(3)				p< 0.001	p< 0.001	p< 0.001
	% of change (1)		-46.28	-38	+21.9	-15.6	-18
	% of change (2)			+15.4	+126.9	+57	+52.6
	% of change (3)				+96.6	+36	+32
Kidney U/g	Mean ±SE	22.4±1.37	10.3±0.6	13.08±0.94	25.85±1.02	17.6±1.29	21.36±1.2
	Significance(1)		p< 0.001	p< 0.005	p>0.05	p<0.05	p> 0.05
	Significance(2)			p< 0.05	p< 0.001	p< 0.005	p< 0.001
	Significance(3)				p< 0.001	p< 0.05	p< 0.005
	% of change (1)		-54	-41.6	+15.4	-21.4	-4.6
	% of change (2)			+26.9	+150.9	+70.8	+107
	% of change (3)				+97.6	+34.5	+63.3

Non – significantp>0.05, significant p< 0.05, highly significant p<0.001.
Significance (1): from G1. Significance (2): from G2. Significance (3): from G3.
%of change (1): different from G1. % of change (2): different from G2. % of change (3): different from G3.

Table (6): Effect of BPF_7on glutathione s-transferase enzyme activity U/g in tissue of stomach of male mice treated with indomethacin daily and day after the other for 15 days in different groups.

parameters		(G1) Control	(G2) INDO daily	(G3) INDO alternative	(G4) BPF_7	(G5) INDO+ BPF_7 daily	(G6) INDO+ BPF_7 alternative
Stomach U/g	Mean ± SE	21.26±1.22	11.43±0.89	14.55±1.11	22.1±0.87	19.9±0.36	20.06±0.97
	Significance(1)		p< 0.005	p<0.01	P>0.05	P>0.05	P>0.05
	Significance(2)			p< 0.05	p< 0.001	p< 0.001	p< 0.001
	Significance(3)				p< 0.005	p< 0.005	p< 0.05
	% of change (1)		-46	-31.5	+3.95	-6.39	-5.6
	% of change (2)			+27	+93	+74	+75.5
	% of change (3)				+51.9	+36.7	+37.8

Non – significantp>0.05, significant p< 0.05, highly significant p<0.001.
Significance (1): from G1. Significance (2): from G2. Significance (3): from G3.
%of change (1): different from G1. % of change (2): different from G2. % of change (3): different from G3.

Table (7): Effect of BPF_7on catalase enzyme activity U/g in tissue of liver and kidney of male mice treated with indomethacin daily and day after the other for 15 days in different groups.

parameters		(G1) Control	(G2) INDO daily	(G3) INDO alternative	(G4) BPF_7	(G5) INDO+ BPF_7 daily	(G6) INDO+ BPF_7 alternative
Liver U/g	Mean ±SE	7.15±0.55	3.71±0.31	4.84±0.39	7.51±0.72	5.65±0.69	6.92±0.31
	Significance(1)		p< 0.005	p< 0.05	p>0.05	p>0.05	p>0.05
	Significance(2)			p< 0.05	p< 0.005	p< 0.005	p< 0.001
	Significance(3)				p< 0.05	p< 0.05	p< 0.05
	% of change (1)		-48	-32.3	+5	-4.19	-3.2
	% of change (2)			+30.4	+102.4	+84.6	+86.5
	% of change (3)				+55	+41.5	+42.9
Kidney U/g	Mean± SE	7.7±0.41	3.96±0.31	4.5±0.41	7.88±0.51	6.36±0.48	7.46±0.37
	Significance(1)		p< 0.001	p< 0.005	p>0.05	p>0.05	p>0.05
	Significance(2)			p>0.05	p< 0.001	p< 0.005	p< 0.001
	Significance(3)				p< 0.005	p< 0.05	p< 0.005
	% of change (1)		-48.7	-41.3	+1.9	-17.7	-3.49
	% of change (2)			+14.3	+98.9	+60.6	+88.3
	% of change (3)				+73.9	+40.3	+64.6

Non – significantp>0.05, significant p< 0.05, highly significant p<0.001.
Significance (1): from G1. Significance (2): from G2. Significance (3): from G3.
%of change (1): different from G1. % of change (2): different from G2. % of change (3): different from G3.

Table (8): Effect ofBPF_7on catalase enzyme activity U/g in tissue of stomach of male mice treated with indomethacin daily and day after the other for 15 days in different groups.

Non – significantp>0.05, significant p< 0.05, highly significant p<0.001.
Significance (1): from G1. Significance (2): from G2. Significance (3): from G3.
%of change (1): different from G1. % of change (2): different from G2. % of change (3): different from G3.

parameters		(G1) Control	(G2) INDO daily	(G3) INDO alternative	(G4) BPF_7	(G5) INDO+ BPF_7 daily	(G6) INDO+ BPF_7 alternative
Stomach U/g	Mean ± SE	6±0.46	3.2±0.29	3.8±0.39	7.2±0.34	5.45±0.45	5.9±0.33
	Significance(1)		p< 0.005	p< 0.05	p>0.05	p>0.05	p>0.05
	Significance(2)			p>0.05	p< 0.001	p<0.05	p<0.001
	Significance(3)				p<0.001	p< 0.05	p< 0.05
	% of change (1)		-46.6	-36.6	+20	-12.5	-0.3
	% of change (2)			+18.7	+125	+64	+86
	% of change (3)				+89.4	+38	+57.3

Table (9): Effect ofBPF_7on nitric oxide concentration µmol/L in tissue of liver and kidney of male mice treated with indomethacindaily and day after the other for 15 days in different groups.

parameters		(G1) Control	(G2) INDO daily	(G3) INDO alternative	(G4) BPF_7	(G5) INDO+ BPF_7 daily	(G6) INDO+ BPF_7 alternative
Liver µmol/L	Mean ±SE	76.7±4.2	40.32±1.59	41.08±2.57	61±2.12	58.4±2.5	67.4±2.13
	Significance(1)		p< 0.001	p< 0.001	p<0.05	p< 0.05	p>0.05
	Significance(2)			P>0.05	p<0.001	p< 0.005	p< 0.001
	Significance(3)				p<0.005	p<0.005	p< 0.001
	% of change (1)		-47.4	-46.4	-20.5	-23.8	-12.12
	% of change (2)			+1.88	+51	+44.8	+67
	% of change (3)				+48	+42	+64
Kidney µmol/L	Mean ±SE	69.17±2.35	38.9±1.9	35.38±1.39	70.4±2.0	52.18±1.66	60.36±1.62
	Significance(1)		p< 0.001	p< 0.001	p>0.05	p< 0.005	p> 0.05
	Significance(2)			p>0.05	p<0.001	p< 0.005	p< 0.001
	Significance(3)				p<0.001	p< 0.001	p< 0.001
	% of change (1)		-43.7	-48.8	+1.77	-24.56	-12.7
	% of change (2)			-9	+80.9	+34	+55
	% of change (3)				+98.9	+47	+70.6

Non – significantp>0.05, significant p< 0.05, highly significant p<0.001.
Significance (1): from G1. Significance (2): from G2. Significance (3): from G3.
%of change (1): different from G1. % of change (2): different from G2. % of change (3): different from G3.

Table (10): Effect of BPF_7on nitric oxide concentration µmol/L in tissue of stomach of male mice treated with indomethacin daily and day after the other for 15 days in different groups.

parameters		(G1) Control	(G2) INDO daily	(G3) INDO alternative	(G4) BPF_7	(G5) INDO+ BPF_7 daily	(G6) INDO+ BPF_7 alternative
Stomach U/g	Mean ± SE	63±1.64	37.9±1.77	38±1.92	69.6±2.5	57.8±1.86	61.4±1.56
	Significance(1)		p< 0.001	p<0.001	P>0.05	P>0.05	P>0.05
	Significance(2)			P> 0.05	p< 0.001	p< 0.001	p< 0.001
	Significance(3)				p< 0.001	p< 0.001	p< 0.001
	% of change (1)		-39.8	-39.6	+10.4	-8.25	-2.5
	% of change (2)			+0.26	+83.6	+52.5	+62
	% of change (3)				+83	+52	+61.5

Non – significantp>0.05, significant p< 0.05, highly significant p<0.001.
Significance (1): from G1. Significance (2): from G2. Significance (3): from G3.
%of change (1): different from G1. % of change (2): different from G2. % of change (3): different from G3.

References

Abatan, M. O.; Lateef, I. and Taiwo, V. O. (2006). Toxic effects of non-steroidal anti-inflammatory agents in rats. African Journal of Biomedical Research, **9:**219-223.

Abd El-Hady, F. K.; Hegazi, A. G. and Wollenweber, E. (2007).Effect of Egyptian propolis on the susceptibility of LDL to oxidative modification and antiviral activity with special emphasis on chemical composition. Z Naturforsch, **62:** 645-655.

Abdallah, I. Z. A.; Khattab, H. A. H. and Heeba, G. H. (2011). Gastroprotective effect of *Cordia Myxa L.* fruit extract against indomethacin-induced gastric ulceration in rats. Life Science Journal, **8 (3):** 433-445.

Abdel Galil, G. A. and El-Awdan, S. A. (2012). Anti- inflammatory, gastroprotective and antioxidant activities of grape seed and *Kava kava*plant extracts in rats. Www. Egynattox.Com. Nature and science, **10(3):** 7-15.

Abd-El-Rehim, S. A.(2009). Effect of extracted crude venom of the jellyfish *Cassiopiaandromeda* on recovery from the testicular toxicity induced by chloramphenicol in rats. Egypt. J. Zool., **53:** 371-392.

Adedapo, A. A. and Aiyelotan, O. (2001). Effect of chronic administration of indomethacin on haematological parameters in rats.Afr. J. Biomed. Res., **4:**159-160.

Aebi, H. (1984). Catalase in vitro.Methods of Enzymolology, **105:**121-126.

Ajaikumar, K. B.; Asheef, M.; Babu, B. H. and Padikkala, J. (2005). The inhibition of gastric mucosal injury by*punicagranatumL.* (pomegranate) methanolicextract. J. Ethnopharmacol., **96:**171-176.

Allard, J.; Bule′ on, M.; Cellier, E.; Renaud, I.; Pecher, C.; Praddaude, F.; Conti, M.; Tack, I. and Girolami, J. (2007). ACE inhibitor reduces growth factor receptor expression and signaling but also albuminuria through B2-kinin glomerular receptor activation in diabetic rats. *Am. J. Physiol. Renal*Physiol., **293:** 1083-1092.

Allonso, D.; Khalil, Z.; Satkunanthan, N. and Livett, B. G. (2003). Drugs from the sea: Conotoxins as drugs leads for neuropathic pain and other neurological conditions. Mini Rev. Med. Chem., **3(7):**785-787.

Ames, B. N.; Shigenaga, M. K.; and Hagen, T. M. (1993). Oxidants, anti-oxidants and the degenerative diseases of aging. Proc. Natl. Acad. Sci., **90:** 7915-7922.

Basavraj, S. T.; Fefar, D. T.; Prajapati, K. S.; Jivani, B. M.; Thakor, K. B.; Patel, J. H.; Ghodasara, D. J.; Joshi, B. P. and Undhad, V. V. (2012). Haematobiochemicalalterations induced by diclofenac sodium toxicity in Swiss albino mice. Veterinary World, **5(7):** 417- 419.

Basivireddy, J.; Vasudevan, A.; Jacob, M.; Balasubramanian, K. A. (2002). Indomethacin-induced mitochondrial dysfunction and oxidative stress in villus enterocytes.Biochemical Pharmacology, **64:** 339-349.

Bengtsson, B. O.; Milstein, J. M. and Sherman, M. P. (2006). Indomethacin- associated neutropenia with subsequent gram-negative sepsis in a preterm infant. Cause or coincidence? Journal of Perinatology, **26:** 381-383.

Bradley, P. P.; Priebet, D. A.; Christensen, R. D. and Rothstein, G. (1982). Measurement of cutaneous inflammation: Estimation of neutrophil content with an enzyme marker. J. Invest. Dermatol.,**78:**206-209.

Buttke, T. M. and Sandstorm, P. A. (1994). Oxidative stress as a mediator of apoptosis.Immunol Today, **15:** 7-10.

Cardici, E.; Suleyman, H.; Aksoy, H.; Halici, Z.; Ozgen, U.; Koc, A. and Ozturk, N. (2007). Effects of *Onosmaarmeniacum*root extract on ethanol-induced oxidative stress in stomach tissue of rats. Chem. Boil. Interact.,**170(1):**40-48.

Chattopadhyay, I.; Bandyopadhyay, U.; Biswas, K.; Maity, P. and Banerjee, R. K. (2006). Indomethacin inactivates gastric peroxidase to induce reactive-oxygen-mediated gastric mucosal injury and curcumin protects it by preventing peroxidase inactivation and scavenging reactive oxygen. Free Radic. Biol. Med., **40(8):**1397-1408.

Chihara, K.; Iwaski, J.; Minamitani, N.; Kaja, H.; Mastukura, S.; Tmaki, N.; Mastumoto, S. and Fugita, T. (1982): Effect of vasoactive intestinal polypeptide on growth hormone secretion in perfused acromegalic pituitary adenoma tissues. J. Clin. Endocrinol.Metab.,**54:** 773-779.

Cragg, G. M.; Newman, D. J. (1999). Discovery and development of antineoplastic agents from natural sources. Cancer Invest, **17:**153-163.

Cuthbert, M.F. (1974). Adverse reactions to non-steroidal antirheumatic drugs.Curr. Med. Res. Opin., **2:**600-610.

Danielisova, V.; Gottlieb, M.; Nemethova, M. and Burda, J. (2008). Effects of bradykinin postconditioning on endogenous antioxidant enzyme activity after transient forebrain ischemia in rat.Neurochem. Res., **33:**1057-1064.

Das, D.; Bandyopadhyay, D.; Bhattacharjee, M. and Banerjee, R. K. (1997). Hydroxyl radical is the major cousative factor in stress-induced gastric ulceration. Free Radical Boil. Med., **23:**8-18.

David, C. (2005). Jellyfish stings. Medicine Article, **45(2):** 233-242.

Davies, N. M. (1998). Non-steroidal anti- inflammatory drug-induced gastrointestinalpermeability. Alimentary Pharmacology& Therapeutics,**12:**303-320.

Dengiz, G. O.; Odabasoglu, F.; Halici, Z.; Suleyman, H.; Cadirci, E. and Bayir, Y. (2007). Gastroprotective and antioxidant effects of amiodarone on indomethacin-induced gastric ulcers in rats.Arch. Pharm. Res., **30(11):**1426-1434.

El-Demerdash, E.; El-Mesallamy, H. O.; Abu-Zaid, N. M. and Gad, M. Z. (2010): The potential therapeutic effect of nitric oxide modulators inexperimentally-induced gastric ulcers. Drug Discoveries & Therapeutics, **4(4):**276-284.

Elliot, S. N. and Wallace, J. L. (1998). Neutrophil-mediated gastrointestinal injury.Canadian journal of Gastroenterology, **12:**559-568.

El-Maddawy, Z. K. H. and El-Ashmawy, I. M. (2013). Hepato-renal and hematological effects of diclofenac sodium in rats.Global Journal of Pharmacology, **7(2):**123-132.

El-Missiry, M. A.; El-Sayed, I. H. and Othman, A. I. (2001). Protection by metal complexes with SOD-mimetic activity against oxidative gastric injury induced byindomethacin and ethanol in rats. Ann. Clin. Biochem.,**38:** 694-700.

El-Saadani, M. A. (2004).A scorpion venom peptide fraction induced prostaglandin biosynthesis in Guinea pig kidneys: Incorporation of ^{14}C-linoleic acid. J. Biochem., Tokyo, **135(1):** 109-116.

El-Sheikh, A. A. K. and El-Moselhy, M. A. (2014). Gastro-protection of atorvastatin in indomethacin-induced ulcer: role of tumor necrosis factor–alpha and prostaglandins. Asian J. Pharmaceut. Res. Health Care.,**6(2):** 15-20.

Enjalbert, A.; Arancibia, S.; Ruberg, M.; Priam, M.; Bluet-Pajot, M. T.; Rotsztein, W. H. and Kordon, C. (1980). Stimulation of in *vitro* prolactin release by vasoactive intestinal peptide. Neuroendocrinology, **31:**200-204.

Ferreira, S. H. (1965). Abradykinin potentiating factor (BPF) present in the venom of *Bothrops jararaca*. Br. J. Pharmacol., **24:**163-169.

Figge, H. L. and Figge, J. (1990). The effects of amiodarone on thyroid hormone function: a review of the physiology and clinical manifestations. J. Clin. Pharmacol.,**30:**588-595.

Frawley, L. S. and Neill, J. D. (1981). Stimulation of prolactin secretion in rhesus monkeys by vasoactive intestinal polypeptide. Neuroendocrinology, **33:**79-83.

Ganong, W. F. (1995). Qouted from review of medical physiology, 17th Ed., Lange, Med. Public., Chapter,19**,** pp**.** 306-326.

Garrel, C.; Ceballos-Picot, I.; Germain, G. and Al-Gubory, K. H. (2007). Oxidative stress-inducible antioxidant adaptive response during prostaglandin F2 alpha-induced luteal cell death in *vivo*. Free Radic. Res., **41:**251-259.

Gill, T. S.; Ponde, J. and Tewari, H. (1991). Effects of endosulfan and phosphamidon poisoning on the peripheral blood of fish (*BarbusConchoniusHammilto*n) J. Environ. Sci. Health., **26 (2):** 249-255.

Gilman, A. G.;Goodman L. S.;Rall, T. W. and Murad, F. (1985). Goodman and Gilman's.The Pharmacological basis of therapeutics, 7th Ed. Macmillan publishing Co.New York, 56: 695-697.

Gürbüz, V.; Alican, I.; Berrak; Yegen, C.; Bozkurt, A.; Oktar, B.; Haklar, G.; Yüksel, M. and Kurtel, H.(1999). Role of nitric oxide in indomethacin-induced gastric mucosal dysfunction in the rat. Exp. Physiol., **84:**319-332.

Habig, W. H.; Pabst, M. J. and Jakoby, W. B. (1974). Glutathione s-transferases: The first enzymatic step in mercapturic acid formation. J. Biol. Chem., **249:**7130-7139.

Harold, S. and Ballard, M. D. (1997). The hematological complications of alcoholism. Alcohol Health& Research World, **21(1):** 42-52.

Higgs, G. (1984). Non-steroidal anti-inflammatory drugs. In textbook of Immunopharmacology; edited by Dole, M. M. and Foreman, J. C.; Blackwell Scientific Publication, Oxford, London, Edinburgh, **67:**305-314.

Hoffbrand, A. V. and Petti, J. E. (1993). Essential hematology.3rd ed. Ltd, Blackwell science. Ltd, **3:** 121-124.

Homem de Bittencourt, Jr. P. I.; Miyasaka, C. K.; Curie, R. and Williams, J. F. (1998). Effects of the antiproliferativecyclopentenone prostaglandin A1 on Glutathione metabolism in human cancer cells in culture. Biochemistry and Molecular Biology International, **45(6):** 1255-1264.

Horton, J. W. & Walker, P. B. (1993). Oxygen radicals, lipid peroxidation and permeability changes after intestinal ischemia and reperfusion.Journal of Applied Physiology, **74**:1515-1520.

Hsu, D. Z. and Liu, M. Y. (2004). Involvement of nitric oxide in gastrin protection of epinephrine in endotoxin intoxication in rats. Toxicology, **204:**203-208.

Jeffrey, T. (2005). Coelentrate and jellyfish envenomations. Med. Art., **21:** 27-36.

Jimeno, J.; Faircloth, G.; Fernández Sousa-Faro, J. M.; Scheure, P.; Rinehart, K.(2003). New marine derived anticancer therapeutics-a journey from the sea to clinical trials. Mar. Drugs., **2:** 14-29.

Juengel, J. L.; Garverick, H. A.; Johnson, A. L.; Youngquist, R. S. and Smith, M. F. (1993). Apoptosis during luteal regression in cattle.Endocrinology, **132:** 249-254.

Kanwar, S.; Tepperman, B. L.; Payne, D.; Sutherland, L. R. & Kubes, P. (1994). Time course of nitric oxide production and epithelial dysfunction during ischemia/reperfusion of the feline small intestine.Circulatory shock, **42**: 135-140.

Kato, H.; Sugino, N.; Takiguchi, S.; Kashida, S. and Nakamura, Y. (1997). Roles of reactive oxygen species in the regulation of luteal function. Rev.Reprod., **2:**81-83.

Khattab, M. M.; Gad, M. Z.and Abdallah, D.(2001). Protective role of nitric oxide in indomethacin-induced gastric ulceration by a mechanism independent on gastric acid secretion.Pharmacol Res, **43:**463-467.

Kornberg, A. and Rachmilewitz, E. A. (1982).A plastic anaemia after prolonged ingestion of indomethacin.Acta.Haematol.,**67(2):** 136-8.

Kubes, P. (1993). Ischemia-reperfusion in feline small intestine: A role for nitric oxide. American journal of physiology,**264:** G143-149.

Lanas, A.; Bajador, E.; Serrano, P.; Fuentes, J.; Carreno, S.; Guardia, J.; Sanz, M.; Montoro, M. and Sainz, R. (2000). Nitrovasodilators, low-dose aspirin, other non-steroidal anti-inflammatory drugs and the risk of upper gastrointestinal bleeding. N. Eng. J. Med. **343(12):**834-839.

Levant, A.; Levy, E.; Argaman, M. and Fleisher-Berkovich, S. (2006). Kinins and neuro-inflammations: Dual effect on prostaglandin synthesis. Eur. J. Pharmacol., **7:** 54-60.

Ma, L. and Wallace, J. L. (2000). Endothelial nitric oxide synthase modulates gastric ulcer healing in rats. Am J. PhysiolGastrointest. Liver Physiol., **279:**G341- G346.

Mates, J. M.; Perez-Gomez, C. and Nudez de Castro, I. (1999). Anti-oxidant enzymes and human diseases.Clinical Biochemistry, **32:**595-603.

Mayer, A. M. S. and Hamann, M. T. (2002). Compounds with antibacterial, anticoagulant, antifungal, antihelmintic, anti-inflammatory, antiplatelet, antiprotozoal and antiviral activities affecting the cardiovascular, endocrine, immune and nervous systems and other miscellaneous mechanism of action. Comp.Biochem. Physiol. C Toxicol.Pharmacol.,**132:** 315-339.

Mayer, A. M. S.; Lehmann, V. B. K. (2001). Antitumor and cytotoxic compounds.Anticancer Res, **21:** 2489-2500.

Mayer, A. M. S.; Rodríguez, A. D.; Berlinck, R. G. S.; Hamann, M. T. (2009). Marine compounds with anthelmintic,antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis and antiviral activities; Affecting the cardiovascular, immune and nervous systems, and other miscellaneous mechanisms of action. Biochim.Biophys. Acta, **1790:** 283-308.

Mayer, A. M. S.and Lehmann, V. K. B. (2000).Marine compounds with antibacterial anticoagulant, antifungal, anti-inflammatory, antimalarial, antiplatelet, antituberculosis and antiviral activities: Affecting the cardiovascular, immune and nervous systems and other miscellaneous mechanisms of action. Pharmacologist, **42:** 62-69.

McLean, P. G.; Ahluwalia, A.; Perretti, M.(2000). Association between kinin B1 receptor expression and leukocyte trafficking across mouse mesenteric postcapillaryvenules. J. Exp. Med.,**192 (3):** 367-447.

Montgomery, H. A. C. and Dymock, J. F. (1961). The determination of nitric oxide in water.Analyst, **86:** 414-416.

Montogomery, R. E. X.; Dryer, R. L.; Conway, T. W. and Spector, A. A. (1980). Biochemistry, A case oriented approach.Third edition, P. 586-612. Toronto-London: The C. V. Mosbycompany.

Naito, Y.; Yoshikawa, T.; Yoshida, N. and Kondo, M. (1998). Role of oxygen radical and lipid peroxidation in indomethacin-induced gastric mucosal injury. Dig. Dis. Sci., **43:** 30-34.

Nilsson, E.; Edenius, C. and Lindgren, J. A. (1995). Ethanol affects leukotriene generation and leukotriene-induced functional responses in human polymorphonucleargranulocytes. Scandinavian Journal of Clinical and Laboratory Investigation, **55(7):** 589-596**.**

Peng, M. Y.; Zhao, X. L.;Gao, X. and Lei, H. Y. (2006). Renin angiotensin system in bone marrow of patients with aplastic anemia.Zhongguo Shi Yan Xue Ye XueZaZhi, **14(3):**512-515.

Piron, M.; Loo, M., Gothot, A.; Tassin, F.; Fillet, G. and Beguin, Y. (2001). Cessation of intensive treatment with recombinant human erythropoietin is followed by secondary anemia. Blood, **97(2):**422-480.

Proksch, P.; Edrada-Ebel, R. A.; Ebel, R. (2003). Drugs from the sea-opportunities and obstacles.Mar. Drugs, **1:** 5-17.

Rabinovitz, M.; Van Thiel, D. H. (1992). Hepatotoxicity of non-steroidal anti-inflammatory drugs.American Journal of Gastroenterology, **87:** 1696-1704.

Rich, B. R. and Cheras, P. A. (2009). The Blue Jelly fish-A Promising Autoimmune stimulant.Rural Industries Research and Development Corporation.http://rirdc.infoservices.com.au/downloads/09-035.pdf.au/downloads/09-035.pdf.

Robert, A. (1981). Acurrent history of cytoprotection.International work-shop on protective actions of prostaglandins on the gastrointestinal mucosa. Prostaglandins, **21:** 89-96.

Samson, W. K.; Burnton, K. P.; Reeves, J. P. and MC.Cann, S.M. (1982). Vasoactive intestinal peptide stimulates luteinizing hormone-releasing hormone release frommedian eminence synaptosomes. Endocrinology, **2:**253-264.

Sankar, R.;Murugan, A. and Sivakumar, V. (2013). Anti-inflammatory, anti-ulcer, antipyretic, analgesic and CNS stimulant activities of marine bryozoan zoobotryon verticillatum.Pharmacologia, 15-21.

Seibert-K; Zhang-Y; Leahy-K; Hauser-S; Masferrer-J; Perkins-W; Lee-L; Isakson-P (1994). Pharmacological and biochemical demonstration of the role of cyclooxygenase 2 in inflammation and pain. Proc. Natl. Acad. Sci., U.S.A.,**91 (25):** 1203-1210.

Seleem, A. A. (2003). Effect of a natural bradykinin potentiating factor on cadmium toxicity during embryogenesis of white rat. M. SC. Thesis. Fac. of Science South Valley Univ., Sohag.

Shridar, N. B. and Narayanan (2007). Toxicity study of diclofenac in claves. Indian Veterinary Journal, **84:** 141-143.

Silva, M. A. ; Rao, V. S.; Souza, C. M.; Neves, J. C. S.; Menezes, D. B.; Santos, F. A. and Andrade, G. M. (2012): Evaluation of thalidomide against indomethacin-induced small intestinal damage and systemic toxicity in rats. Biomedical Research, **23(1):** 125-133.

Slomiany, B. L.; Piotrowski, J.and Slomiany, A. (1999). Endothelin-1 interleukin-4 and nitric oxide synthase modulators of gastric mucosal injury by indomethacin: Effects of antiulcer agents. J. Physiol. Pharmacol.,**50:** 197-210.

Strom, B. L.; Carson, J. L.; Schinnar, R.; Snyder, E. S.; Shaw, M. and Lundin, F. E. Jr. (1993). Non-steroidal anti-inflammatory drugs and neutropenia. Archives of Internal Medicine, **153:**2119-2124.

Tripp, M. A. and Tepperman, B. L. (1995). Effect of nitric oxide on integrity, blood flow and cyclic GMP levels in the rat gastric mucosa: modulation by sialoadenectomy. Br. J. Pharmacol., **115(2):**344-348.

Vijayan, E.; Samson, W. K.; Said, S. I. and Mccann, S. M. (1979). Vasoactive intestinal peptide: Evidence for a hypothalamic site of action to release growth hormone, luteinizing hormone, and prolactin in conscious ovariectomized rats. Endocrinology, **104:**53-57.

Whittle, B. J. R. and Vane, J. R. (1983). Prostacyclin, thromboxanes and prostaglandins-action and roles in the gastrointestinal tract.In progress in Gastroenterology, Grune and Stratton.Inc. New York, PP. 3-30.

Wolfe, M. M.; Lichtenstein, D. R. and Singh, G. (1999). Gastrointestinal toxicity of non-steroidal anti-inflammatory drugs. New England Journal of Medicine, **340:** 1888-1899.

Yoshikawa, T.; Naito, Y.; Kishi, A.; Tomii, T.; Kanek, T.; Linvma, S.; Ichikawa, H. ; Yasuda, M.; Takahashi, S. and Kondo, M.(1993). Role of active oxygen, lipid peroxidation and antioxidants in the pathogenesis of gastric mucosal injury induced by indomethacin in rats. Gut, **34:**732-737.