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Combined Gum Acacia of Meloxicam therapy versus Meloxicam monotherapy : A Biochemical and Histopathological Study

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Abstract

Objective: To study the protective action of Gum Acacia against the damaging effects of,meloxicam on intestine and digestive enzymes

Study design: This study was performed on thirty albino rats divided into three groups each group contains 10 rats, the first group treated with meloxicam only , the second group treated with meloxicam and Gum Acacia and the third group acts as controls .After 21 days of feeding, all rats were killed, the activity of digestive enzymes ; lipase (intestinal & pancreatic), amylase(pancreatic & intestinal).Also lactate dehydrogenase (LDH) & alkaline phosphatase (ALP) activities were assayed .In addition, the histopathological examination of intestinal tissues were carried out.

Results: The first group showed a significant decrease ($P<0.001$) in pancreatic lipase and amylase activities together with a significant increase ($P<0.001$) in the intestinal amylase, lipase, alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) activities when compared with controls. The second group showed a significant increase ($P<0.001$) in pancreatic and intestinal lipase and amylase activities as well as in intestinal ALP and LDH activities when compared to the controls. Histopathologically, there were an intestinal epithelial damage (shedding of the mucosa with focal inflammation) in meloxicam treated group.
But, the co-treated rat group displayed small changes of denuded intestinal mucosa..

Conclusion: Our study concluded that gum acacia exhibits a protective action that can antagonize the damaging effects of meloxicam therapy.
Key words: Meloxicam-Gum acacia-Digestive enzyms activities- Biochemistry-Histopathology.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) cause intestinal damage as an adverse reaction in both experimental animals and humans (Bjarnason *et al.*,1998 and Tanaka *et al.*, 2002a). Although a number of elements such as bacterial flora, neutrophils and inducible nitric oxide synthase (iNOS) are involved in the pathogenesis of these lesions (Asako *et al.*, 1992; Yamada *et al.* , 1993 and Konaka *et al.*, 1999), a deficiency of endogenous prostaglandins (PGs) is of a prime importance in the background for the ulcerogenic response to meloxicam as a novel anti-inflammatory drug. This contention is supported by the fact that meloxicam-induced gastric and intestinal damage which has been prevented by supplementations with exogenous prostaglandins (Kunikata *et al.*, 2002a; Tanaka *et al.*, 2002b).

Meloxicam acts primarily through the inhibition of cyclo-oxygenase (COX) enzyme, which is involved in the arachidonic acid metabolism and exists as a constitutive COX-1 and an inducible COX-2 .isoform *(Vane,*1971;*Tanaka et al., 2001).*

On the other hand. Guar gum has been used to treat diabetes to curb the appetite and to carry toxins out of the body. Consumption of gum acacia stimulated intestinal and splenic immune system function in rats. The effects of gum acacia consumption on cholesterol levels have been equivocal as one study documented lowered serum cholesterol levels (Ross *et al.*, 1983), while another one documented no or inconsistent effects (Eastwood *et al.*, 1986).

This study aims to clarify the role of

gum aqueous extracts in its therapeutic dose on pancreatic and intestinal enzymes activity in meloxicam treated rats as well as to illustrate functional and biochemical changes together with the associated histopathological alterations following meloxicam therapy.

Material And Methods

Animal Groups:

Thirty male albino rats weighing 200 gms were divided into three groups each of which contains ten animals. The first group was received meloxicam in its diet (15 mg/ day); the second was taken meloxicam(200 mg/kg b.w. / day) followed by gum acacia (1 gm / day).The drug was given in each group for a period of 21 days; the third group(controls) were placed on normal diet and water *ad libtum.* All rats were killed by decapitation and exsang-uinations: they were always killed at 9 am to avoid possible diurnal variation in enzy-me levels (Potter and Ono , 196I) and after 24 hours of last dosage for rats which receive medications. Pancreas and jejunum,5-7cm long segment, were immediately excised. The intestinal segments were flushed with ice cold 0.9% saline. The segments were then cut open' longitudinally and the mucosa was scraped with microscopic slide (Shurolhchundro *et al.,* 1995).

Enzyme Assays:

The pancreas and mucosal scrapings were homogenized in cold 0. 25 M sucrose in Teflon coated motor driven homogenizer so as to prepare a 5% homogenate. The homogenate was centrifuged at 5000 xg for 15 minutes in a cooling centrifuge (5^0C), supernatant collected,frozen in sample vials and stored at (-20 °C), until assayed (Dehnath *et al,*2007).

Lactate dehydrogenase which has enzyme commission number (E.C.1.1.1.27). Total lactate dehydrogenase activity was measured by the colorimetric procedure of Moore and Yontz (1969) by using sodium pyruvate as substrate Amylase (E.C. 3.2.1.1) activity was assayed with 2% (w/v) starch solution as substrate (Rick and Stegbauer. 1974). The 2% starch solution was prepared in phosphate buffer (pH 7). The reaction mixture was incubated at 37°C for 30 min. Then dinitrosalicylic acid (DNS) was added to stop the reaction and kept in boiling water bath for 5 min . After cooling. reaction mixture is diluted with distilled water and absorbance recorded at 540 nm. Activity was determined from the maltose standard curve and expressed as mole of maltose released from starch/min/mg protein at 37°C.

Lipase (E.C.3.1.1.3) activity was determined based on Cherry and Candell (1932). The quantity of fatty acid released in unit time is measured by the quantity of NaOH required to maintain constant pH. The reaction mixture consisted of distilled water, tissue homogenate, phosphate buffer solution (pH 7) and olive oil emulsion. The mixture was shaken well and incubated at 4 °C for 24 h. Then 95% alcohol and 2 drops of phenolphthalein indicator were added and titrated against 0.05 N NaOH until the appearance of permanent pink color. A control was taken using enzyme source that was inactivated prior to addition of buffer and olive oil emulsion. The milliequivalent of alkali consumed is taken as a measure of the activity of the enzyme.

Alkaline phosphatase (ALP) (E.C. 3.1.3.1) activity was determined by **Garen and Levinthall(1960).** The assay mixture consisted of bicarbonate buffer (0.2M, pH 9.5), 0.1 M $MgCl_2$, tissue homogenate and freshly prepared 0.1 M para-nitrophenyl phosphate (*p*-NPP) as substrate. The reaction mixture was incubated in water bath at 37°C for 15 min and then stopped with 0.1 N NaOH. Optical density was recorded at 410 nm. ALP activity was expressed as nanomoles *p*-nitrophenol released/min/mg protein at 37°C.

Tissue protein content was determined following the standard method **(Lowry *et al.,* 1951)** and expressed as mg protein/g wet tissue.

Histopathological technique:

Jejunal specimens fixed in Bouin's solution for 24 hours, dehydrated in ascending grades of ethyl alcohol (70%,80%, 90% ,95%),then cleared in terpinol and embedded in paraffin and sectioned at 6 urn, The sections were deparaffinized in xylene, embedded in descending grades of ethyl alcohol, washed in water and then stained with Haemat-

oxylin & Eosin (Tanaka *et al.*, 2002 a)

Statistical Analysis:

Statistical evaluation was made in Windows Vista, using SPSS16.0 software and Student T test and Wilcoxon tests for nonparametric data. For analysis of correlation between the values, Pearson correlation analyses were used. Data were expressed as mean ± SD. Differences at the level of $P < 0.05$ were considered statistically significant

Results

The first group (treated with meloxicam alone) when compared with controls showed a significant decrease in the activities of both pancreatic lipase and amylase (16.32 ± 0.76 vs 20.82 ± 0.87 & 37.75 ± 0.52 vs 41.72± 2.1 and P<0.0001 &P<0.001 respectively) also there were significant increase in the mean values of the following enzymatic activities: intestinal lipase(42.16 ± 2.02 vs 33.49 ± 1.40, P<0.0001) intestinal amylase (13.74 ± 0.46 vs 10.99 ± 0.59 P<0.001) , ALP(1.82 ± 0.29 vs 0.69 ± 0.06 , P<0.0001) and LDH(95.3 ± 4.92 vs 55.8 ± 1.75, P<0.0001) Table 1&Fig 1

The second group (treated with meloxicam followed by Gum Acacia) when compared with controls revealed a significant increase in all enzymatic activities as follows: pancreatic lipase (27.74 ± 1.45 vs 20.82 ± 0.87, P<0.0001); pancreatic amylase (43.93 ± 2.10 vs 41.72± 2.1, P<0.001), intestinal lipase (43.44 ± 5.97 vs 33.49 ± 1.40,P<0.0001), intestinal amylase (14.81 ± 1.26 vs 10.99 ± 0.59, P<0.001), ALP(0.99 ± 0.10 vs 0.69 ± 0.06, P<0. 01) and LDH(64.61 ± 2.17 vs 55.8 ± 1.75, P<0.0001) Table 2 & Fig.2

There were a significant differences in the second group enzymatic activities when compared to the first one There were very high significant increase in pancreatic lipase (P<0.0001), high significant increase in pancreatic amylase(P<0.001),significant increase in intestinal lipase(P<0.01), significant increase in intestinal amylase (P<0.01),however there were high significant decrease in ALP(P<0.001) and very high significant decrease in LDH(P<0.0001).

From the histopathologic view, our study revealed focal ulceration, desquamation & shedding of the intestinal mucosa with marked alterations of villous morphology and decreased its height, a moderate to intense inflammatory infiltration of the mucosa & submucosal as well as vasodilatation, congestion and edema in the interstitium and lamina propria in the first group specimens(Figs.5-7).Second group specimens showed focal superficial erosions with a minor inflammatory infiltration of the intestinal mucosa, however, the villous height was more or less normal and the villi showed well defined arrangement (Fig.4).

Table 1: Comparison between mean of enzyme activities of the 1st (meloxicam treated) group and controls (data as mean ± S.D)

Biochemical marker	Meloxicam treated group(n=10)	Controls(n=10)	P-value
Pancreatic lipase	16.32 ± 0.76	20.82 ± 0.87	P<0.0001*** decreased
Pancreatic amylase	37.75 ± 0.52	41.72± 2.1	P<0.001** decreased
Intestinal lipase	42.16 ± 2.02	33.49 ± 1.40	P<0.0001*** increased
Intestinal amylase	13.74 ± 0.46	10.99 ± 0.59	P<0.001** increased
ALP(tissue homogenate)	1.82 ± 0.29	0.69 ± 0.06	P<0.0001*** increased
LDH(tissue homogenate)	95.3 ± 4.92	55.8 ± 1.75	P<0.0001*** increased

Activities are expressed as follows : lipase as units/mg protein; amylase as micromol of maltose released /min/g protein; ALP as nanomoles *p*-nitrophenol released /min/mg protein at 37°C and LDH as μmol of pyruvate reduced/min/mg protein at 37°C.

***=very high significant ; **= high significant ; n= number of cases

Table 2 :Comparison between mean of enzyme activities of the 2nd (treated with

meloxicam followed by Gum Acacia) group and controls (data as mean ± S.D)

Biochemical marker	2nd group (n=10)	Controls (n=10)	P-value
Pancreatic lipase	27.74 ± 1.45	20.82 ± 0.87	P<0.0001*** increased
Pancreatic amylase	43.93 ± 2.10	41.72± 2.1	P<0.01* increased
Intestinal lipase	43.44 ± 5.97	33.49 ± 1.40	P<0.0001*** increased
Intestinal amylase	14.81 ± 1.26	10.99 ± 0.59	P<0.001** increased
ALP(tissue homogenate)	0.99 ± 0.10	0.69 ± 0.06	P<0.01* increased
LDH(tissue homogenate)	64.61 ± 2.17	55.8 ± 1.75	P<0.0001*** increased

Activities are expressed as follows : lipase as units/mg protein; amylase as micromol of maltose released /min/g protein; ALP as nanomoles *p*-nitrophenol released /min/mg protein at 37°C and LDH as μmol of pyruvate reduced/min/mg protein at 37°C.
***=very high significant ; **=high significant ;*=significant ; n= number of cases

Table 3: Comparison between mean of enzyme activities of the 1st (meloxicam treated) group and 2nd (treated with meloxicam followed by Gum acacia) group (data as mean ± S.D)

Biochemical marker	2nd group(n=10)	1st group(n=10)	P-value
Pancreatic lipase	27.74 ± 1.45	16.32 ± 0.76	P<0.0001*** increased
Pancreatic amylase	43.93 ± 2.10	37.75 ± 0.52	P<0.001** increased
Intestinal lipase	43.44 ± 5.97	42.16 ± 2.02	P<0. 01* increased
Intestinal amylase	14.81 ± 1.26	13.74 ± 0.46	P<0.01* increased
ALP(tissue homogenate)	0.99 ± 0.10	1.82 ± 0.29	P<0. 01** decreased
LDH(tissue homogenate)	64.61 ± 2.17	95.3 ± 4.92	P<0.0001*** decreased

Activities are expressed as follows : lipase as units/mg protein; amylase as micromol of maltose released /min/g protein; ALP as nanomoles *p*-nitrophenol released /min/mg protein at 37°C and LDH as μmol of pyruvate reduced/min/mg protein at 37°C.
***=very high significant ; **=high significant ;*=significant ; n= number of cases

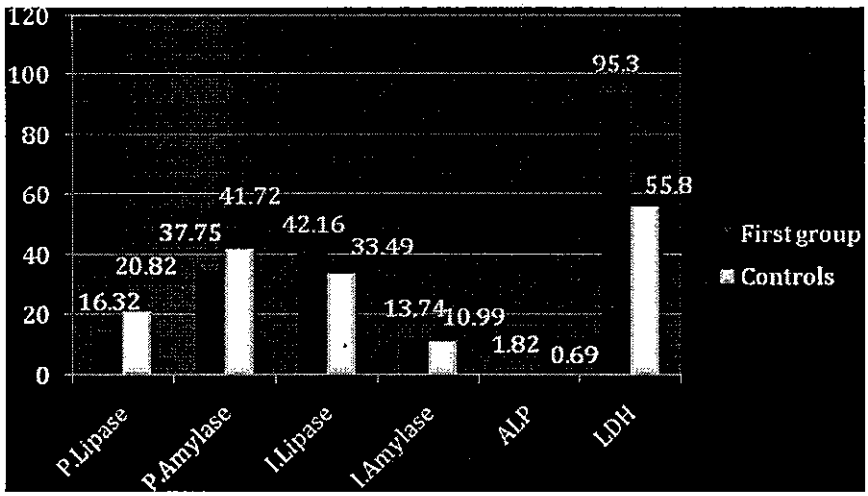

Fig.(1): Comparison between mean of enzyme activities of the 1st (meloxicam treated) group and controls

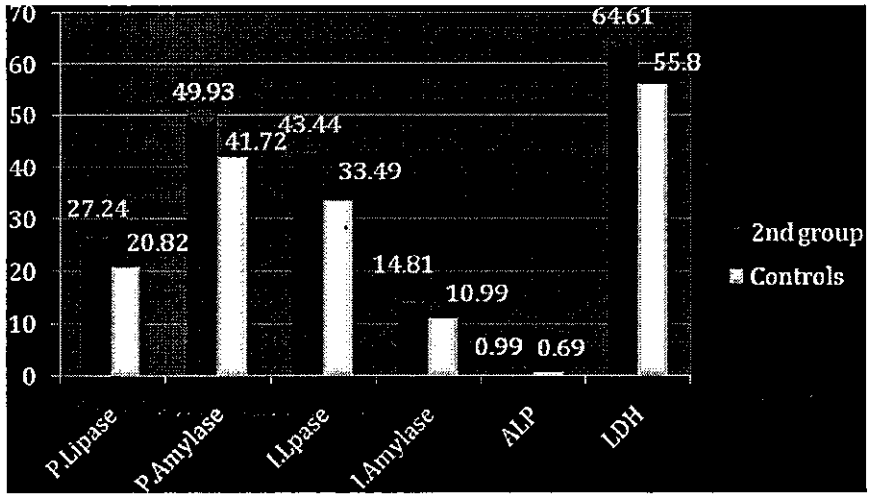

Fig.(2): Comparison between mean of enzyme activities of the 2nd (treated with meloxicam followed by Gum Acacia) group and controls

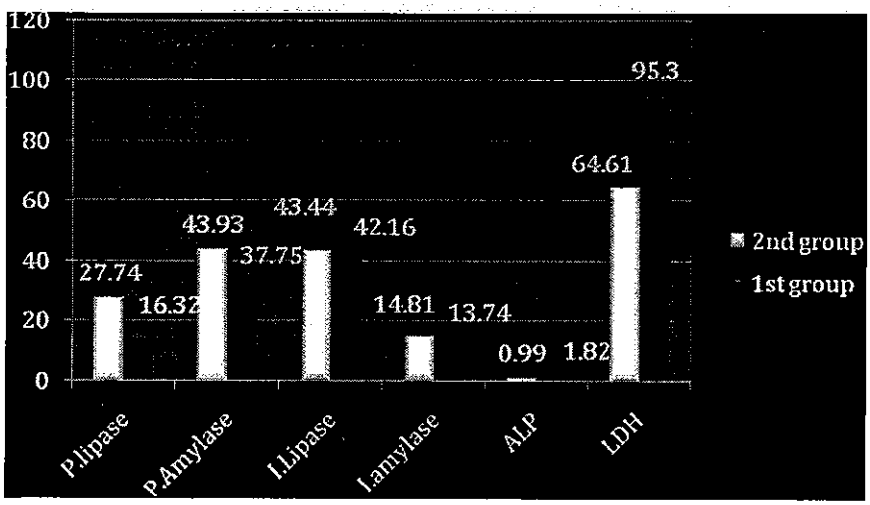

Fig.(3): Comparison between mean of enzyme activities of the 2nd (treated with meloxicam Followed by Gum acacia treated) group and 1st (meloxicam treated) group

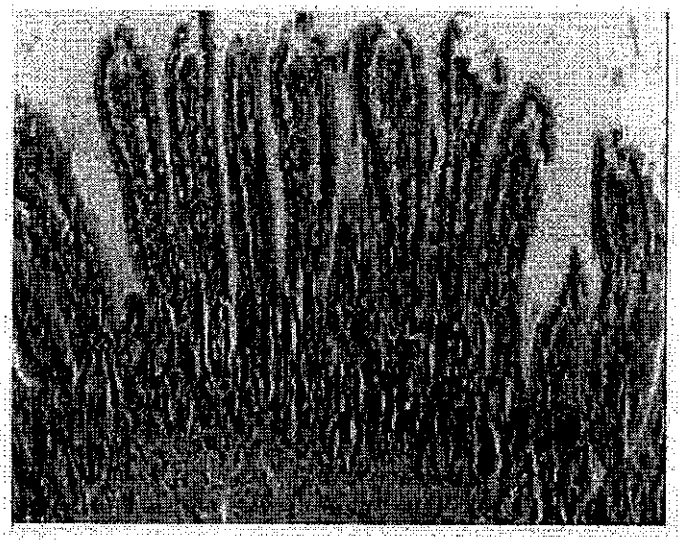

Fig.(4): Epithelial cells shed from the top of villi with almost inflammatory cell infiltration normal villous height and well defined arrangement of villi (H.&E. x100)

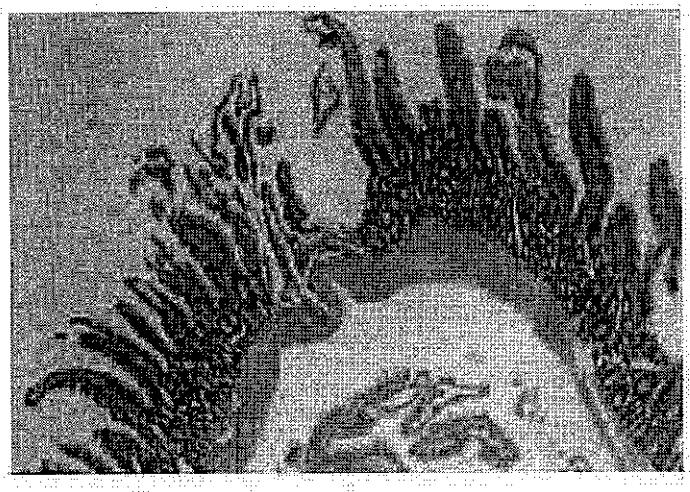

Fig.(5): Markedly altered villous morphology and decreased height. Note the focal mucosa ulcer with exposure of submucosal interstitium and disarrangement of villi. (H. &E. x 100

Fig.(6): Marked alterations of villous morphology occurred including mucosal atrophy, fusion of adjacent villi, inflammatory cell infiltration, and vascular dilatation, congestion and edema in the villous interstitum and lamina propria. (H.&E.x100)

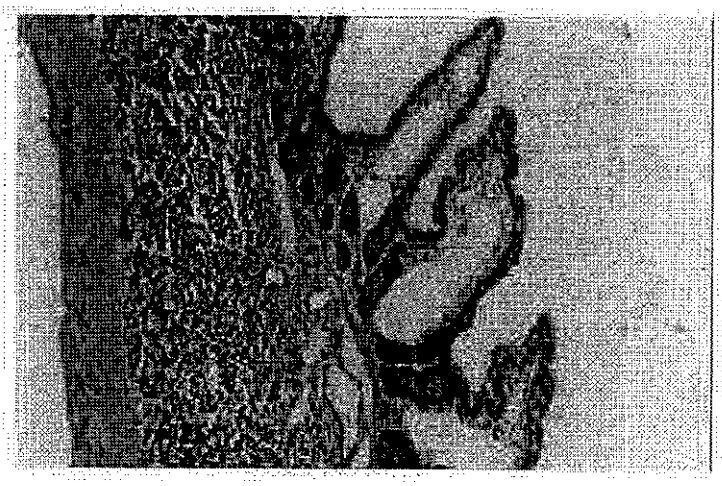

Fig.(7):Dilatation of central chyle duct of jejunal mucosa(H.&E. x 100).

Discussion

This study displayed affection of both intestinal mucosa and brush border together with a significant increase in the activities of the brush border enzymes (lipase, amylase, alkaline phosphatase & lactate dehydrogenase) after 21 days of meloxicam therapy, either alone or in combination with gum compared to control group. These results coincided with those reported by Dory *et al.* (2002) and Tanaka *et al,* (2002a) who confirmed that the inhibition of both Cox-1 and Cox-2 is required for the induction of intestinal damage. Because the inhibition of Cox-1 only [inspite causing intestinal hypermotility, bacterial invasion and increase inducible nitric oxide synthase (iNOS) expression that leads to upregulates of Cox-2 expression and the prostaglandin E_2 (PGE_2)] produced by Cox-2 may counteract subsequent events such as increase of iNOS activity and maintain the mucosal integrity. Also, PGE_2 counteract increases in myeloperoxidase enzyme.

This enzyme is a heme-containing enzyme that present only in phagocytic cells (predominantly neutrophils)and is responsible for the green colour of pus, act on H_2O_2 to produce hypohalous acid ,which is a powerful toxin oxidizing many Fe and S-containing groups, oxidatively decarboxylating and deaminating proteins as well as cleaving peptide bonds.(Marks ***et al.,*** 2005)

$$H_2O_2 + Cl^- + H^+ \xrightarrow{\text{Myeloperoxidase}} HOCl + H_2O$$

This sequence of events may explain why intestinal damage occurs only when both *Cox-l* and Cox-2 are inhibited. ***Lichtenberger el al.*** (1995) suggested that NSA1Ds have a detergent-like action which disrupts mucus gel and/or cell membrane integrity of the gastrointestinal tract .The decreased activity of brush border enzyme; alkaline phosphatase is consistent with this suggestion, although no significant structural changes were seen on electron microscopy.

Moreover, acidic NSAIDs may concentrate in the mucosa (Szabo *et al.,* 1989). Non-steroidal anti-inflammatory drugs (NSAIDs) can damage the stomach as well as the small and large intestines causing ulceration, chronic bleeding and eventually iron deficiency (Davies. 1995 and Bertschinger *et al.,* 1996). Also, iron deficiency may be associated with oxidative DNA damage, cognitive dysfunction, anemia and compromised immune function (Ames, 1999). In addition, this study revealed a significant decrease in the pancreatic enzymes activities (lipase & amylase) after 21 days of meloxicam *and a significant increase in this enzymes activities after the same duration of* meloxicam-gum combined therapy when compared to controls. These findings were mimic what was noticed by Insel (1996) Garavito and Mulichak (2003)

Conventional NSAIDs at an ulcerogenic dose caused a marked hypermotility in the rat small intestine. This

change in the motility occurred within 20 to 30 minutes, much sooner than the onset of bacterial invasion and other inflammmatory changes as well as the development of intestinal damage. Because abnormal contraction of the intestinal wall results in disruption of the unstirred mucus layer over the epithelium, leading to increased mucosal susceptibility to pathogens and irritants, the intestinal hypermotility may play a role in the pathogenic mechanism of meloxicam-induced small intestinal lesions. When the intestinal hypermotility as well as the bacterial invasion and other inflammatory changes were potently inhibited, this would prevent the intestinal damage (Kunikata *et al.,* 2002a, b).

Wallace et al., (2000) reported that SC-560 (a selective Cox-I inhibitor) produced a decrease in gastric mucosal blood flow suggesting that the effect of NSAIDs on the mucosal blood flow is brought about by suppression of Cox-1.Also,intestinal hypermotility induced by Cox-1 inhibitor caused mucosal hypoxia and microvascular injury due to smooth muscle contraction (Anthony *et al.*, 1997). Moreover, Wallace *et al.* (2000) displayed that celecoxib (a selective Cox-2 inhibitor) increased neutrophils adherence in mesenteric venules. These blood cells play a permissive role in NSAID-induced intestinal damage that was significantly prevented by anti-neutrophil serum *(Konaka et al.,* 1999). In addition, neutrophils are a source of oxygen radicals and inducible nitric oxide synthase (iNOS).The interaction of nitric oxide with superoxide anion(O_2^-) forms peroxynitrites that may be detrimental in the above mentioned gastrointestinal lesion model (Zang *et al.*,2000).Thus, Tanaka *et al* .(2002a) assumed that

Cox-2 contributes to maintaining the integrity of the intestinal mucosa through inhibition of neutrophils migration under the inhibition of Cox-I.

Most protease activities reduced in the presence of 0.5% gum sonicate with trypsin-like activities of β-gingivalis and β-intermedia organisms. The gum soluble fraction was nearly always less inhibitory than the sonicate one. Acacia gum is an anti-ulcer drug by virtue of its various effects on mucosal offensive and defensive factors. Also, its action against these periodontal pathogens and their enzymes suggests that it may be of clinical value (Clark *et al.,* 1993).

Gum resins are applied to the inspissated milky juices of certain plants. When they are finely powdered and rubbed down with water, they form emulsions and used chiefly in medicine *(*Han *et al.,* 1999). Gums are a high energy food source composed mainly of water, complex polysaccharides, calcium and trace minerals (iron, aluminum, silicon, potassium, magnesium and sodium). Arabic gum (Acacia gum) has a property to bind cations especially divalent ones. As a result, the amount of calcium and magnesium in the caecum rises considerably to be efficiently absorbed from the large bowel enhancing the healing of the gastrointestinal ulcers. This is provided by a fact that gum was found to be transformed into a gelatinous state at a higher level in the intestine and to be transported more rapidly through the alimentary tract (Wapinir *et al.,* 1996).

Histopathology In our study was carried out on the principle tissue (intestinal tract) and revealed marked changes; ulceration , inflammatory infiltration, disturbed villous height & morphology, vascular dilatation with congestion and edema in the interstitium and lamina propria of the intestinal wall of rats treated with meloxicam and mild pathological changes; superficial ulceration and minor inflammation in the animals receiving combined meloxicam and gum therapy.
These data were similar to those observed by ***Goel*** and *Bhattacharya(1991)*; Kunikata *et al.*(2002a) & Tanaka *et al.*(2002a). The formers also found that gum does not disintegrate or decompose appreciably in the alimentary tract and it absorbs a large quantity of water, therefore, acting as a mechanical laxative. In addition, gum tends to increase fecal nitrogen excretion, does not affect starch digestion and does not inhibit the utilization of vitamin A; one of the essential factors in ulcer healing.

This study concluded that gum acacia provides a protection and defense against the harmful effects of meloxicam therapy used as one of the novel antiCox-1 and Cox-2 NSAIDs.

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العلاج بخليط من الصمغ العربى والميلوكسيكام فى مقابل العلاج بالميلوكسيكام فقط: دراسه كيموحيويه وهستوباثولوجيه

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من أقسام الكيمياء الحيويه الطبيه والباثولوجى *والتشريح** والهستولوجى *** بطب الأزهر-بنين(أسيوط والقاهره)

بالرغم من التأثيرات العلاجيه العديده لميلوكسبكام إلا أن هذه الماده لها تأثيرات هدامه على القناه الهضمية مثل القرح والندوب والنزيف ، وهذه الدراسه نفذت على ثلاثه مجموعات لذكور الجرذان متساويه الوزن كل منها تشمل عشره جرذان أعطيت المجموعه الأولى غذاء يحتوي على 15 مجم فى اليوم من الميلوكسيكام يوميا، بينما خضعت المجموعة الثانية لغذاء يحتوي على ميلوكسيكام (بنفس التركيز السابق) مع صمغ بجرعه 1جم فى اليوم فى غذائهم أما المجموعة الثالثه لم تعط أي أدوية(مجموعه ضابطه) وكل مجموعة فحصت بعد إحدى وعشرون يوما فوجد انخفاض ملحوظ فى نشاط إنزيمي الليبيز والأميليز البنكرياسي مع زيادة فى نشاط إنزيمات الليبيز والأميليز والفوسفاتيز القاعدي واللاكتات ديهدروجينيز المعوي في المجموعة الأولى التي أعطيت ميلوكسيكام إذا ما قورنت بالمجموعة الضابطة أما المجموعة الثا نيه التى أعطيت ميلوكسيكام مع الصمغ فأتضح أن هناك زيادة هامة في متوسط نشاط إنزيمات البنكرياس والأمعاء إذا ما قورنت بالمجموعة الضابطة. وبالنسبة للتغيرات الهستوباثولوجية فقد وجد تقرح مع التهابات موضعية فى الغشاء المبطن للأمعاء بالمجموعة الأولى وبعض التغيرات مثل ضعف فى الغشاء المخاطى للأمعاء فى المجموعة الثانيه مما سبق نستنتج أن الصمغ العربى له تأثيرواقى يضاد التأثيرات الهدامة للعلاج بالميلوكسيكام.