Research Results in Pharmacology

Research Results in Pharmacology 8(3): 63–69
UDC: 615.015.2:615.065
DOI 10.3897/rrpharmacology.8.81003

Research Article

Efficiency evaluation of Amlodipine combined with N-acetylcysteine on Indomethacin-induced gastritis in rats

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Academic editor: Oleg Gudyrev ♦ **Received** 21 January 2022 ♦ **Accepted** 8 August 2022 ♦ **Published** 25 August 2022

Citation: Annouf Y, Al laham S, Chatty E (2022) Efficiency evaluation of Amlodipine combined with N-acetylcysteine on Indomethacin-induced gastritis in rats. Research Results in Pharmacology 8(3): 63–69. https://doi.org/10.3897/rrpharmacology.8.81003

Abstract

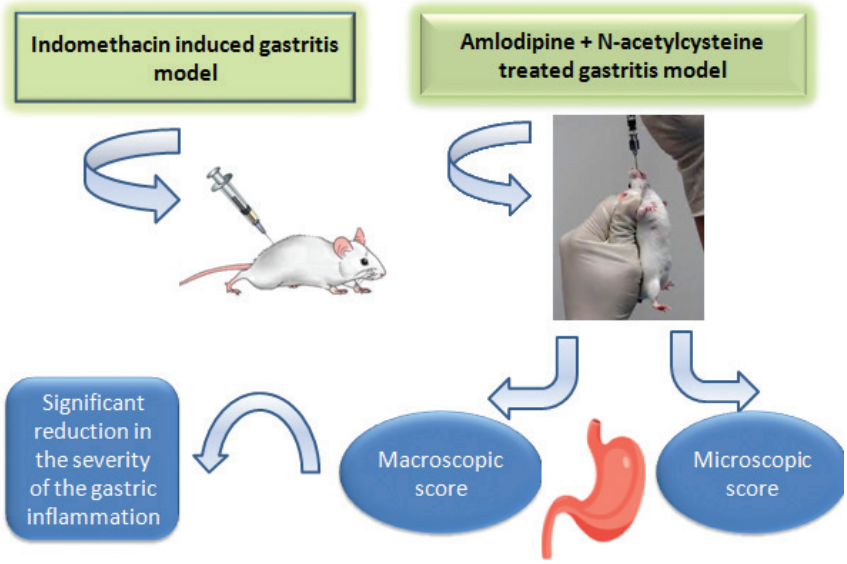
Introduction: It is a well-known phenomenon that nonsteroidal anti-inflammatory drugs cause gastric mucosal damage. Amlodipine is a third generation dihydropyridine-type calcium channel blocker; it can inhibit inflammatory cytokines and enhance antioxidant defenses. N-acetylcysteine can act both as a precursor of reduced glutathione and as a direct ROS scavenger. Moreover, N-acetylcysteine has been purported to have anti-inflammatory properties.

Materials and methods: 34 albino Wistar rats were used. The model of gastritis was induced by subcutaneous Indomethacin prepared in 5% sodium bicarbonate administered at a dose rate of 9 mg/kg for two days at 24h intervals. N-acetylcysteine (500 mg/kg), Amlodipine (10 mg/kg) and N-acetylcysteine (500 mg/kg) combined with Amlodipine (5 mg/kg) were administrated for seven consecutive days beginning 24 h after the first Indomethacin injection. Rats were sacrificed under ether anesthesia on the 8th day. The stomach injury was assessed by macroscopic damage and histological study.

Results and discussion: The results showed that macroscopic stomach damage scores caused by administration of Indomethacin did not significantly decrease by administration of N-acetylcysteine alone ($p>0.05$), but it decreased significantly by administration of Amlodipine alone or by its combination with N-acetylcysteine ($p<0.05$). Microscopic stomach damage scores did not significantly decrease by administration of Amlodipine or N-acetylcysteine alone ($p>0.05$), but they decreased significantly by administering the combination of Amlodipine with N-acetylcysteine ($p<0.05$). Administration of Amlodipine with N-acetylcysteine showed significant reduction in the severity of the gastric inflammation induced by Indomethacin, which was evidenced macroscopically and microscopically.

Conclusion: This study concluded that administration of Amlodipine with N-acetylcysteine produce obvious enhancement in gastritis induced by Indomethacin.

Graphical abstract:



Keywords

Amlodipine, gastritis, histological study, macroscopic damage, N-acetylcysteine, Nonsteroidal anti-inflammatory drugs.

Introduction

The term gastritis has been used loosely to clarify vague endoscopic findings of the gastric mucosa (eg. erythema, nodularity, and erosions) and additionally to elucidate gastric inflammation from mucosal injury. Accurately, gastritis refers to the microscopic returns of gastric mucosal injury with inflammation (Francis 2008). Infectious (Helicobacter pylori), chemical, and autoimmune are the most common shapes of gastritis (Rugge and Graham 2016). Chemical gastropathy may be seen in three clinical settings: postgastrectomy alkaline reflux; bile reflux secondary to gastroduodenal dysmotility; and administration of aspirin or NSAID (Washington and Peek 2009).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are thought to be the most widely used drug group worldwide (Hawkins 2000). It is a well-known phenomenon that NSAIDs cause gastric mucosal damage resulting in consequences ranging from nonspecific dyspepsia to ulceration, upper gastrointestinal (GI) bleeding and death – summarized by the term 'NSAID gastropathy' (Becker et al. 2004).

The conventional view is that NSAID-induced mucosal damage results from inhibition of cyclo-oxygenase with consequent weakness of reparative prostaglandin generation. NSAIDs may also affect the gastric mucosal barrier by altering mucus and bicarbonate secretion and by intervening with mucosal blood flow (Quinn et al. 1993). In addition to inhibiting cyclooxygenase and decreasing prostaglandin production, NSAIDs stimulate mucosal damage *via* ROS produced by recruited leukocytes. Reactive oxygen species (ROS) lead to apoptosis and mucosal injury by mitochondrial damage as well as lipid, protein, and DNA damage (Suzuki et al. 2012).

Amlodipine is a third generation dihydropyridine-type calcium channel blocker commonly used for the treatment of hypertension (Mohammed et al. 2016). Experimental studies have shown that Amlodipine can inhibit inflammatory cytokines and boost antioxidant defenses (El Morsy et al. 2015).

N-acetylcysteine (NAC), a precursor of reduced glutathione (GSH), has been used clinically for more than 30 years, primarily as a mucolytic. NAC is also used in conditions characterized by decreased GSH or oxidative stress (Kelly 1998). Moreover, NAC has been purported to have anti-inflammatory properties. NAC inhibits induction of the Activator Protein-1 (AP-1) and NF-κB (Atalay et al. 2016).

The present study highlights the effect of Amlodipine combined with N-acetylcysteine on Indomethacin-induced gastritis in rats.

Materials and methods

Materials

Indomethacin (FarmaSino Pharmaceuticals, Jiangsu, China), N-acetylcysteine (Wuhan Grand Hoyo Company Ltd, China), Amlodipine (Prudence Pharma Chem, Ankleshwar, India).

Animals and experimental design

Wistar albino rats weighing 160–290 g were purchased from the Scientific Research Center, Damascus, Syria. The animals were supplied with ad libitum feed and water. The animals were kept under the controlled environmental conditions (temperature 23±2 °C, humidity 55±15%, lighting regimen of 12h light:12h dark). They were adapted for one week before any experiments.

The animals were randomly divided into five groups:

Group I: 6 rats received the vehicle (physiological saline) orally and served as normal control group.

Group II: 7 rats received subcutaneous Indomethacin prepared in 5% sodium bicarbonate, administered at a dose rate of 9 mg/kg for two days at 24h intervals and served as Indomethacin control group (Annouf et al. 2020). It also received physiological saline orally.

Group III: 8 rats were administered N-acetylcysteine dissolved in physiological saline (500 mg/kg body weight, po) (Lee and Kang 2019) for seven consecutive days, beginning 24h after the first Indomethacin injection.

Group IV: 6 rats were administered Amlodipine dissolved in physiological saline (10 mg/kg body weight, po) (El Morsy et al. 2015) for seven consecutive days, beginning 24h after the first Indomethacin injection.

Group V: 7 rats were administered 500 mg/kg of N-acetylcysteine plus 5 mg/kg of Amlodipine for seven consecutive days, beginning 24h after the first Indomethacin injection.

Groups III, IV and V were given 9 mg/kg of subcutaneous Indomethacin for two days at 24h intervals.

On the 8th day, each sub group of animals across all groups was sacrificed. The stomach was isolated and was opened along greater curvature, then washed in saline solution and any macroscopic change was checked. A precise evaluation of the lesions was made after each specimen was fixed in 10% formalin.

Macroscopic score

All macroscopic evaluations were performed just after scarification of the rats and before sending half of the stomach to the physiology laboratory (Sabiu et al. 2015) (Table 1).

Table 1. Macroscopic inflammation assessment of the stomach

Score	Remark
0	Almost normal mucosa
1	Vascular congestions
2	One or two lesions
3	Severe lesions
4	Very severe lesions
5	Mucosa full of lesions

Histopathological observations

Tissue samples were collected from one half of the stomach and were kept for histologic assessment. Five micrometer sections were gained from paraffin-embedded tissues and stained with hematoxylin and eosin. Tissue slides were tested under a light microscope.

The following histological features were examined by an unbiased pathologist blinded to the experimental design: grade and type of inflammation, extension of inflammation throughout the gastrointestinall wall (mucosa, submucosa, muscular layer and serous membrane), existence of lymphatic follicle, necrosis, granuloma, cryptitis, crypt abscess, and epithelial lesions (erosions, ulcers) (Nakhai et al. 2007) (Table 2).

Table 2. Microscopic inflammation assessment of the stomach

Criteria	Score
Increased inflammatory infiltration	0 (none)
	1 (mild)
	2 (moderate)
	3 (severe)
Lymphoid aggregate/follicle	0 (none)
	1 (recognized)
Necrosis	0 (none)
	1 (recognized)
Granuloma	0 (none)
	1 (recognized)
Cryptitis	0 (none)
	1 (recognized)
Crypt abscess	0 (none)
	1 (recognized)
Erosions	0 (none)
	1 (recognized)
Ulcers	0 (none)
	1 (recognized)
Transmural inflammation	0 (none)
	1 (recognized)
Maximum score	11

Statistical analysis

Data analyses were done using a software program Graph Pad Prism version 8. Data were expressed as mean±SEM, and different groups were compared using Kruskal-Wallis test followed by Dunn's test for multiple comparisons for non-parametric data. P values were considered statistically significant when they were less than 0.05.

Results

Macroscopic score

No stomach sections from normal control group revealed any morphological changes. In contrast, subcutaneous injection of Indomethacin caused damage in the stomach. Vascular congestions, hemorrhagic spots, and erosions were noticed. The morphological score in the

Indomethacin control group was significantly increased (p=0.0020) as compared to normal control group.

The group treated with Amlodipine reduced the severity of the gross lesion. There was statistical significance when compared with Indomethacin control group (p=0.0186).

NAC-treated group reduced the severity of the macroscopic score, but there was no statistical significance when compared with Indomethacin control group (p=0.0685).

Amlodipine-combined-with-NAC-treated group revealed reduction in the severity of the gross lesion. There was statistical significance when compared with Indomethacin-treated group (p=0.0060), but there was no statistical significance when compared with Amlodipine-treated

Table 3. Macroscopic score of different experimental groups

Group Macroscopic Score	Normal control group	INDO control group	NAC treated group	AML treated group	AML+NAC treated group
0	6 (100%)	1 (14.29%)	4 (50%)	5 (83.335)	7 (100%)
1		4 (57.14%)	4 (50%)		
2		2 (28.57%)		1 (16.67%)	
3					
4					
5					

Note: INDO - Indomethacin, NAC - N-acetylcysteine, AML - Amlodipine

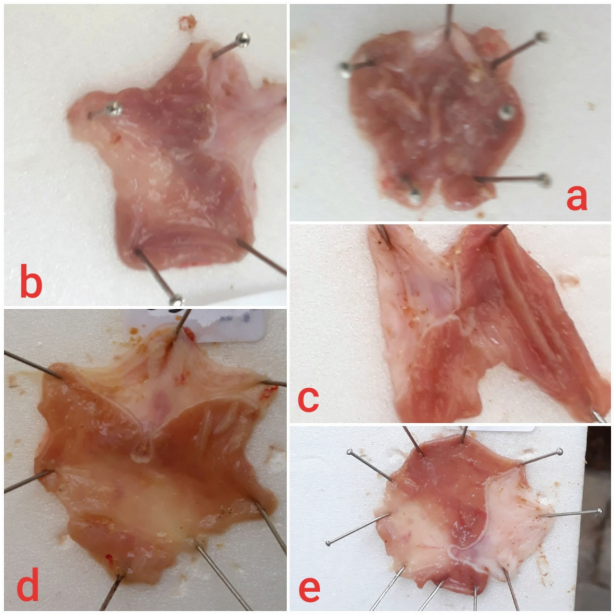


Figure 1. Macroscopic appearance of the stomach: **a.** Normal control group (score=0); **b.** Indomethacin control group (score=2); **c.** Amlodipine-treated group (score=0); **d.** N-acetylcysteine-treated group (score=1); **e.** Amlodipine+N-acetylcysteine-treated group (score=0).

group (p=0.7730), and NAC-treated group (p=0.1630) (Table 3) (Fig. 1).

Microscopic score

The stomach specimen of all rats from normal control group revealed an intact architecture. On the other hand,

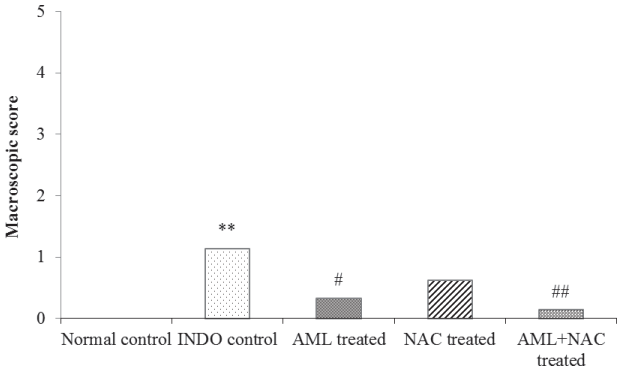


Figure 2. Effect of N-acetylcysteine combined with Amlodipine on macroscopic score in Indomethacin-induced gastritis in rats. Data are expressed as mean±SEM. **Note:** ** - Significant difference as compared to normal control group at p<0.01; # - Significant difference as compared to Indomethacin control group at p<0.05; ## - Significant difference as compared to Indomethacin control group at p<0.01; INDO - Indomethacin, NAC - N-acetylcysteine, AML - Amlodipine.

the stomach specimen of Indomethacin control group revealed increased inflammatory cell infiltration; the inflammation was mild to moderate; it also revealed lymphatic follicle and cryptitis in some of them. There was statistical significance when compared with normal control group (p=0.0084).

Administration of Amlodipine as therapy revealed in some rats reduction in the severity of the in the stomach injury with no statistical significance when compared with Indomethacin control group (p=0.0989).

Administration of NAC as therapy also revealed in some rats reduction in the severity of the stomach injury with no statistical significance when compared with Indomethacin control group (p=0.3101).

Administration of Amodipine with NAC revealed reduction in the severity of the stomach injury (Fig. 3) (Table 4) with statistical significance when compared with Indomethacin control group (p=0.0095), but no statistical significance was observed when compared either with NAC-treated group (p=0.0958), or with Amlodipine-treated group (p=0.3990) (Fig. 4).

Discussion

The NSAID-related gastroduodenal injury is very frequent and the most dangerous complication of any drug therapy. The NSAID gastropathy is considered a “silent epidemic” and, therefore, has been an area of intense research. Among the commonly used NSAIDs, Indomethacin (INDO) possesses the highest ulcerogenic potential to humans. The major reason for gastric pathogenesis caused by NSAIDs including INDO is reduced prostaglandin (PG) synthesis by inhibition of the cyclooxygenases (COXs) (Yadav et al. 2012). There are principally three different mechanisms of NSAID-induced GI complications: inhibition of enzyme COX-1 and gastroprotective PG,

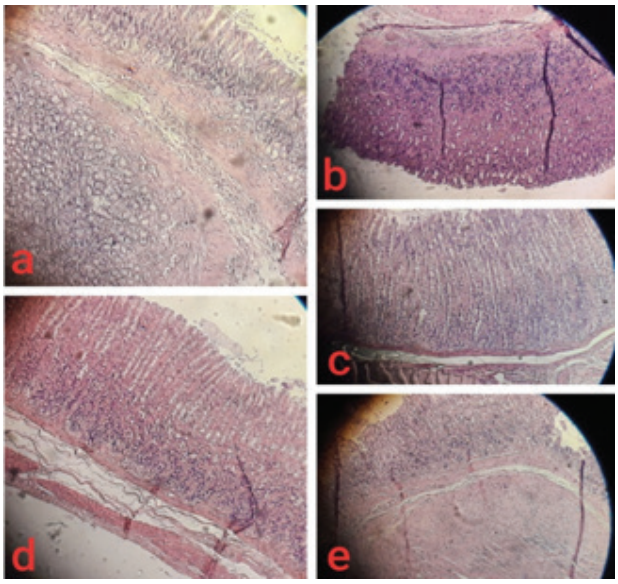


Figure 3. Histological appearance of stomach tissue sections, original magnification ×10. Note: **a.** Normal control group (grade 0) shows an intact architecture; **b.** Indomethacin control group (grade 3) shows focal cryptitis and increased inflammatory cells infiltration; **c.** Amlodipine-treated group (grade 2) shows non specific chronic inflammation; **d.** N-acetylcysteine (500 mg/kg) treated group (grade 2) shows increased inflammatory cells inflitration; **e.** Amlodipine+N-acetylcysteine-treated group (grade 0) shows an intact architecture.

Table 4. Microscopic score of different experimental groups

Group Microscopic Score	Normal control group	INDO control group	NAC treated group	AML treated group	AML+NAC treated group
0	6 (100%)	1 (14.29%)	3 (37.5%)	4 (66.67%)	6 (85.71%)
1		2 (28.57%)	2 (25%)		
2		2 (28.57%)	2 (25%)	1 (16.66%)	1 (14.29%)
3		2 (28.57%)	1 (12.5%)	1 (16.66%)	
4					
5					
6					
7					
8					

Note: INDO - Indomethacin, NAC - N-acetylcysteine, AML - Amlodipine.

membrane permeabilization, and production of additional proinflammatory mediators (Sinha et al. 2013). INDO is a known inducer of reactive oxygen and nitrogen species in animal models, which may contribute to mucosal injury (Yadav et al. 2012). Till now, no effective treatment has been yet developed for addressing the NSAID-related gastric damage (Sinha et al. 2013).

Amlodipine is acalcium channel blocker (Sheraz et al. 2016). All the knowledge from the literature shows that calcium ions play the main role in the synthesis and release of inflammatory mediators which cause inflammation (Unlu et al. 2013). Therefore, a decrease in intracellular calcium levels may prevent or reduce inflammation. Amlodipine exerts anti oxidative effects in vitro and in vivo by inhibiting the oxidizability of the cell membrane and low-density lipoproteins. This effect was mediated by

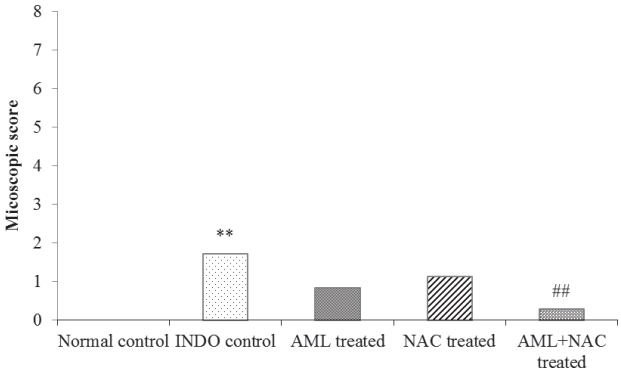


Figure 4. Effect of N-acetylcysteine combined with Amlodipine on microscopic score in Indomethacin-induced gastritis in rats. Data are expressed as mean±SEM. **Note:** ** - Significant difference as compared to normal control group at $p<0.01$; ## - Significant difference as compared to Indomethacin control group at $p<0.01$; INDO - Indomethacin, NAC - N-acetylcysteine, AML - Amlodipine.

removal free radicals due to its highly lipophilic properties and its chemical structure (El Morsy et al. 2015).

N-acetylcysteine is a source of sulfhydryl groups in cells and a scavenger of free radicals as it interacts with reactive oxygen species (ROS), such as hydrogen peroxide and hydroxyl radical. Therefore, NAC has an important role in prevention of oxidative stress (Hou et al. 2015). There are several reports about the role of NAC in inflammation. In vitro studies report on the inhibitory effect of NAC on a series of inflammatory cytokines, inflammatory cell accumulation and migration (Sadowska and Backer 2007). NAC used at clinically obtainable concentrations can inhibit both neutrophil and monocyte chemotaxis. The inhibition of chemotaxis by NAC was pH- and concentration-dependent (Kharazmi and Nielsen 1988). NAC inhibits the induction of the Activator Protein-1 (AP-1) and NF-κB. These transcription factors are induced in response to oxidative stress, supporting the argument that the anti-inflammatory properties of NAC are due to its mechanism of action as an antioxidant (Atalay et al. 2016).

This study highlights the effect of Amlodipine combined with N-acetylcysteine on NSAIDs-induced gastritis in rats.

In this study, Indomethacin-induced gastritis was revealed macroscopically and microscopically. Administration of Amlodipine alone showed significant reduction in the severity of the macroscopic score, but it cause no significant reduction in the severity of microscopic score. This finding was in discord with many studies, such as the study by Patil et al that showed that Amlodipine could reduce the ulcer index and gastric pH in rats with gastric ulcer (Patil et al. 2012). In addition, the study by Behave et al that proved that Amlodipine produces a significant protective effect on gastric ulceration and also produces significant anti-ulcer effects when used in combination with famotidine and omeprazole (Bhave et al. 2006).

This study also showed that N-acetylcysteine administration alone produced no significant reduction in the

gastric injury induced by Indomethacin. There was no significant reduction in the severity of macroscopic and microscopic score when N-acetylcysteine was administered alone. This finding was in discord with the study by Farinati et al that revealed that NAC is fairly well tolerated and apparently leads to an endoscopic, symptomatic, and to some extent histologic improvement that is not clearly related to changes in mucosal GSH and MDA levels in patients with gastritis and non-ulcer dyspepsia (Farinati et al 1997).

Administration of Amlodipine with NAC showed significant reduction in the severity of the gastric inflammation induced by Indomethacin that was evidenced macroscopically and microscopically.

Conclusion

Administration of Amlodipine with NAC produces obvious enhancement in gastritis induced by NSAIDs via anti-inflammatory effects of NAC and Amlodipine. The study suggests investigation of the effect of this combination on oxidative statues by procedure of biochemical assays of enzymatic and non-enzymatic antioxidants in the gastric tissues.

Conflict of interest

The authors declare no conflict of interests.

Acknowledgements

The authors are thankful to Damascus University, Faculty of Pharmacy, for providing funding and the necessary assistance. The authors are also thankful to AL-Assad University hospital for providing the assistance.

References

- Annouf Y, Al-Laham S, Al-Shatti E (2020) Effect of Amlodipine on enteropathy induced by Indomethacin in rats. International Journal of Current Pharmaceutical Research 12(3): 144–150. https://doi.org/10.22159/ijcpr.2020v12i3.38229
- Atalay F, Odabasoglu F, Halici M, Cadirci E, Aydin O, Halici Z, Cakir A (2016) N-acetylcysteine has both gastro-protective and anti-inflammatory effects in experimental rat models: Its gastro-protective effect is related to its in vivo and in vitro antioxidant properties. Journal of Cellular Biochemistry 117(2): 308–319. https://doi.org/10.1002/jcb.25193 [PubMed]
- Becker JC, Domschke W, Pohle T (2004) Current approaches to prevent NSAID-induced gastropathy – COX selectivity and beyond. British Journal of Clinical Pharmacology 58(6): 587–600. https://doi.org/10.1111/j.1365-2125.2004.02198.x [PubMed] [PMC]
- Bhave AL, Bhatt JD, Hemavathi KG (2006) Antiulcer effect of amlodipine and its interaction with H 2 blocker and proton pump inhibitor in pylorus ligated rats. Indian Journal in Pharmacology 38(6): 403–407. https://doi.org/10.4103/0253-7613.28206
- El Morsy EM, Kamel R, Ahmed MAE (2015) Attenuating effects of coenzyme Q10 and amlodipine in ulcerative colitis model in rats. Immunopharmacology and Immunotoxicology 37(3): 244–251. https://doi.org/10.3109/08923973.2015.1021357 [PubMed]
- Farinati F, Cardin R, Libera G Della, Pallotta T, Rugge M, Colantoni A, Gurrieri G (1997) Effects of N-acetylcysteine in patients with chronic atrophic gastritis and nonulcer dyspepsia: a phase III pilot study. Current Therapeutic Research 58(10): 724–733. https://doi.org/10.1016/S0011-393X(97)80106-3
- Francis DL (2008) Gastritis. In: Mayo Clinic Gastroenterology and Hepatology Board Review, United States, 65–67. https://doi.org/10.1201/b14432-9
- Hawkins C (2000) The gastroduodenal toxicity of nonsteroidal anti-Inflammatory drugs. A review of the literature. Journal of Pain and Symptom Management 20(2): 140–151. https://doi.org/10.1016/s0885-3924(00)00175-5 [PubMed]
- Hou Y, Wang L, Yi D, Wu G (2015) N-acetylcysteine and intestinal health: a focus on mechanisms of its actions. Frontiers in Bioscience 20(5): 872–891. https://doi.org/10.2741/4342 [PubMed]
- Kelly GS (1998) Clinical applications of N-acetylcysteine N-acetylcysteine. Alternative Medicine Review 3(2): 114–127. [PubMed]
- Kharazmi A, Nielsen H (1988) N - acetylcysteine inhibits human neutrophil and monocyte chemotaxis and oxidative metabolism. International Journal of Immunopharmacology 10(1): 39–46. https://doi.org/10.1016/0192-0561(88)90148-8 [PubMed]
- Lee SI, Kang KS (2019) N-acetylcysteine modulates lipopolysaccharide-induced intestinal dysfunction. Scientific Reports 9(1): 1–10. https://doi.org/10.1038/s41598-018-37296-x [PubMed] [PMC]
- Mohammed NEM, Messiha BAS, Abo-Saif AA (2016) Effect of amlodipine, lisinopril and allopurinol on acetaminophen-induced hepatotoxicity in rats. Saudi Pharmaceutical Journal 24(6): 635–644. https://doi.org/10.1016/j.jsps.2015.04.004 [PubMed] [PMC]
- Nakhai LA, Mohammadirad A, Yasa N, Minaie B, Nikfar S, Ghazanfari G, Zamani M, Dehghan G, Jamshidi H, Boushehri V, Khorasani R, Abdollahi M (2007) Benefits of Zataria multiflora Boiss in experimental model of mouse inflammatory bowel disease. Evidence-based Complement Alternative Medicine 4(1): 43–50. https://doi.org/10.1093/ecam/nel051 [PubMed] [PMC]
- Patil AN, Advani MG, Mali SN, Pawar S, Raut SB (2012) Evaluation of anti-ulcer effect of amlodipine in gastric ulcer models in rats. Indian Journal of Pharmacology 44(3): 387–389. https://doi.org/10.4103/0253-7613.96344 [PubMed] [PMC]
- Quinn CM, Jarnason B, Price AB (1993) Gastritis in patients on non-steroidal anti-inflammatory drugs. Histopatholog 23(4): 341–348. https://doi.org/10.1111/j.1365-2559.1993.tb01217.x [PubMed]
- Rugge M, Graham DY (2016) Gastritis. In: Practical Gastroenterology and Hepatology Board Review, United States, 126–131. https://doi.org/10.1002/9781119127437.ch20
- Sabiu S, Garuba T, Sunmonu TO, Sulyman AO, Ismail NO (2015) Indomethacin-induced gastric ulceration in rats: Ameliorative roles

of *Spondias mombin* and *Ficus exasperate*. Pharmaceutical Biology 54(1): 180–186. https://doi.org/10.3109/13880209.2015.1029050 [PubMed]

- Sadowska AMÃ, Backer WA De (2007) Antioxidant and anti-inflammatory efficacy of NAC in the treatment of COPD: Discordant in vitro and in vivo dose-effects: A review. Pulmonary Pharmacology & Therapeutics 20(1): 9–22. https://doi.org/10.1016/j.pupt.2005.12.007 [PubMed]
- Sheraz MA, Ahsan SF, Khan MF, Ahmed S, Ahmad I (2016) Formulations of Amlodipine: a review. Journal of Pharmaceutics 2016: 8961621. https://doi.org/10.1155/2016/8961621 [PubMed] [PMC]
- Suzuki H, Nishizawa T, Tsugawa H, Mogami S, Hibi T (2012) Roles of oxidative stress in stomach disorders. Journal of Clinical Biochemistry and Nutrition 50(1): 35–39. https://doi.org/10.3164/jcbn.11-115SR [PubMed] [PMC]
- Sinha M, Gautam L, Shukla PK, Kaur P, Sharma S, Singh TP (2013) Current perspectives in NSAID-induced gastropathy. Mediators of Inflammation 2013: 258209. https://doi.org/10.1155/2013/258209 [PubMed] [PMC]
- Unlu M, Karaman M, Ay SA, Balta S, Cakar M, Demirkol S, Celik T, Arslan E, Demirbas S, Turker T, Yaman H, Bulucu F, Sağlam K (2013) The Comparative Effects of Valsartan and Amlodipine on Vascular Microinflammation in Newly Diagnosed Hypertensive Patients. Clinical and Experimental Hypertension 35(6): 418–423. https://doi.org/10.3109/10641963.2012.739237 [PubMed]
- Washington MK, Peek Jr RM (2009) Gastritis and gastropathy. In: Textbook of Gastroenterology, England, 1005–1025. https://doi.org/10.1002/9781444303254.ch42
- Yadav SK, Adhikary B, Chand S, Maity B, Bandyopadhyay SK, Chattopadhyay S (2012) Free radical biology & medicine molecular mechanism of Indomethacin-induced gastropathy. Free Radical Biology & Medicine 52(7): 1175–1187. https://doi.org/10.1016/j.freeradbiomed.2011.12.023 [PubMed]

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