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PHARMACOLOGICAL REVIEW ON IN VIVO SCREENING MODELS OF ANTIULCER AGENTS AND INDIAN MEDICINAL PLANTS WITH ANTIULCER ACTIVITY

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ABSTRACT

Peptic ulcer is an open sore within the lining of the stomach, duodenum (beginning of the small intestine) or oesophagus. Some medications like non-steroidal anti-inflammatory drugs (NSAIDS) and other drugs induce breakage of mucosa of stomach or duodenum leading to ulcers. A normal stomach maintains a balance between its aggressive and defensive factor ,pathogenesis of ulcer disease includes an imbalance between gastric offensive factors like acid, pepsin secretion, Helicobacter pylori (*H.pylori*), bile salts, ethanol, lipid peroxidation, nitric oxide (NO) and defensive factors like prostaglandins (PG'S), gastric mucus, blood flow, mucosal cell shedding, cellular renovation, glycoproteins, mucin secretion, and antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT)and glutathione levels. There are various modern management methods of ulcer and it includes inhibition of gastric acid secretion, to promote gastro protection, to block apoptosis and stimulate epithelial cell-proliferation for effective healing. Animal models area customed to induce ulcer and assess the anti-ulcer activity of existing drugs as well as newer ones too, Herbal drugs have

preserved their importance because of their relatively less toxicity, better acceptability, compatibility with human body, lesser adverse effects, cost effective, effective and easy availability. Herbs have also proven helpful with treating gastric ulcers in dose dependent manner and may be taken fresh or as dried extracts or tinctures. Preliminary phytochemical screening of those identified the presence of important secondary metabolites like flavonoids and tannins. A spread of nutritional strategies and dietary supplements have a positive impact on reducing the symptoms and retarding the event of gastric ulcers.

In this review attempts are made to summarize anti-peptic activity of assorted medicinal plants which are utilized by rural people, its screening model methods and parameters to be assessed are reported.

Keywords: Peptic ulcer, antiulcer models, shay rat model, NSAIDS, *H. Pylori*

INTRODUCTION

Ulcer is commonly a disorder of gastrointestinal tract which leads to severe discomfort and morbidity. Peptic ulcer is an inflamed lesion or excavation of mucosa occurring either in gastric or duodenum when exposed to acid or pepsin. Damage of mucosa which normally protects the oesophagus, stomach and duodenum from gastric acid and pepsin leads to peptic ulcer **[1]**. Peptic ulcer is because of an imbalance between the defensive (gastric mucus and bicarbonate secretion, innate resistance of the mucosal cells, prostaglandins) factors and also the aggressive (Acid pepsin,and *H. pylori)* factor **[2]**. Despite it occurs at any level of the alimentary tract that's exposed to acid and pepsin, they occur mostly in either the stomach orduodenum in the ratio of 1:4 each of the two main types i.e. acute or chronic. Treatment include **[3]**, Eradicating *H. pylori* infection, Neutralizing the acid after it is released or decreasing secretion of gastric acid, and consuming agents that protect the gastric mucosa from damage. The etiology of peptic ulcer disease is probably due to a combination scenario involving an imbalance between the aggravating factors (HCl, pepsin, ethanol, bile salts, drugs) and the defensive factors (mucus-bicarbonate layer, cellular regeneration, prostaglandins, mucosal blood flow). NSAIDs play a crucial role in the pathogenesis. The pathology is divided in three broad categories, (1) *H. pylori* positive (2) *H. pylori* negative and non-NSAID associated (3) NSAID associated **[4]**.

SCREENING METHODS OF ANTI-ULCER AGENTS [5]

In order to screen anti-ulcer agents, various animal models have been used either by surgical procedures, pharmacological agents, or by inducing stress.

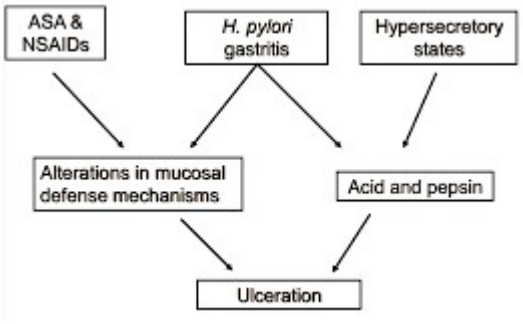

Figure 1: Pathophysiology of Ulcer

Table 1: Various screening methods of anti-ulcer agents

ACUTE ULCER

Parts	Animal	Screening methods
Stomach	Rats	Shay rat ulcers, drug-induced ulcers (NSAIDs,phenylbutazone, histamine, reserpine, serotonin), stress induced ulcers (water-immersion,restraint, cold, exertion, electric shock)
	Guinea pigs	Histamine inducedulcers; aspirin induced ulcers
	Dogs	Aspirin induced ulcers, indomethacin induced ulcers, histamine induced ulcers
Duodenum	Rats	Histamine-carbachol induced ulcers, cysteamine induced ulcers, mepirizole induced ulcers
	Guinea pigs	Histamine induced ulcers, dimaprit induced ulcers, gastrin induced ulcers
	Dogs	Histamine induced ulcer

CHRONIC ULCER

Stomach	Rats	Clamping-cortisone induced ulcers, thermal induced ulcers, thermal-cortisone induced ulcers, acetic acid induced ulcers
	Dogs	Acetic acid induced ulcers, indomethacin induced ulcers, histamine induced ulcers, cinchophen induced ulcers
Duodenum	Rats	Acetic acid induced ulcer
	Dogs	Acetic acid induced ulcer

Pylorus ligated [shay] rat:

Albino rats weighing 150-200 gms are housed in individual cages, Care must be taken to avoid coprophagy and fasted for 24-36 hours prior to pyloric ligation. Rats are anesthetized with low dose of ether, a midline incision below the xiphoid process and the abdomen is cut opened, pyloric portion of the stomach is taken out and ligated avoiding damage to its blood supply or traction to the pylorus. The stomach is replaced and abdominal wall is closed by interrupted sutures. The drugs are administered immediately after pyloric ligation. The animals are deprived of both water and food during the postoperative period and are sacrificed at the end of 19 hours after operation. Stomachs contents are drained into tubes and subjected to analysis for free and total acidity as well pH. The inner surface of the stomach is dissected and is examined for ulceration. The ulcer index is calculated. Usually circular lesions are observed **[43-51]**.

Histamine induced gastric ulcer

Induction of experimental gastric ulcers in various species by histamine administration has been recognized and is mediated also through vasospastic action of histamine, a H^2 receptor agonistin guinea pighistamine produces gastric ulceration in animals along with increase in volume of gastric

secretion and marked enhancement of free total acidity. Male guinea pigs weighing 300-400 g are fasted for 36 hours (water allowed). In order to protect the animal against histamine toxicity, gastric ulceration is induced by injection 1 ml of histamine acid phosphate (50 mg base) i.p. 15 min before and after histamine. The drugs are given p o or s. c. 30-45 min before histamine injection. Four hours after histamine administration, the animals are sacrificed and the stomach is dissected out. The stomach is cut open and gastric contents are subjected to analysis, the degree of ulceration is graded **[39]**.

Dimaprit induced gastric ulcers

Dimaprit also being a H^2 receptor agonist elevates the acid secretion, Dimaprit was administered i.p. or i.v. to 24 h fasted rats and the animals are sacrificed 4 hours after injection. The test drugs are given 30 min 48 before dimaprit. The procedure is extremely simple and rapid. It is very useful for evaluating not only the absolute potency of a drug given by any route but also of other pharmacodynamic parameters particularly the length of action which is an important criterion in selecting novel potentially H_2 antagonistic drugs **[39]**.

Acetic acid induced chronic gastric ulcer

Acetic acid is known to produce ulcers by gastric obstruction ending up torise in acidic gastric juice.Rats are anesthetized with phenobarbitone (35 mg/kg, i.p.), the abdomen of the rat is opened and the stomach is visualized. Gastric ulcers are produced in rats by 50% acetic acid (0.06ml/animal), at the anterior serosal surface of the glandular portion of the stomach 1 cm away from the pyloric end. On 1^{st} day, test drug and standard drug is given orally, 4h after the application of acetic acid and continued for either up to 3 or 7 days after induction of ulcer. The animals are sacrificed after the last dose of test drug i.e. after 18 hrs either on 4th day or 8th day of experiment to examine the ulcer size and healing **[49]**.

Ethanol-induced Mucosal Damage in Rats

This antiulcer model named as ethanol induced mucosal damage, is a model, where ethanol is used in excess amount because ethanol excessive amount causes gastritis which is characterized by sub-epithelial hemorrhages, cellular exfoliation, inflammatory cell infiltration, and mucosal oedema. Albino rats of either sex are divided into 6 groups of animals in each group. The animals are given test drugs or standard drug butdeprived of food for 24 hrs with free access water. 1hr later 1ml/200gm of 99.80% ethanol is administered p.o to each animal. Animal are sacrificed 1 hour later of ethanol administration; stomach is taken out and cut open along the greater curvature and pinned. The length of each gastric lesion is measured in mm. The percentage inhibition

is written as sum of the length of the control-mean lesion index of text / mean lesion index of control × 10 **[40]**.

Indomethacin and Ibuprofen

These are also administration in a similar way. Indomethacin is given in a dose of 10 mg/kg, p.o. and ibuprofen is given in two doses of 200 mg/kg, p.o. with an interval of 15 hours. The animals are sacrificed 6 hours after indomethacin administration and 6 hours after the second dose of ibuprofen. The drugs for 46 studying gastro protective effects are given 30 min before each dose of the ulcerogen. It appears that the development of gastric mucosal damage by aspirin and possible other ulcerogenic NSAIDs, involved hyper production of tissue destructive free **[46, 48]**.

Cysteamine induced ulcer:

Cysteamineis known to increase serum enzyme elevation, it stimulates gastric acid secretion rate and inhibits the alkaline mucus secretion from the Brunner's glands in proximal duodenum. Gastric emptying is also delayed and subsequentlyincreases serum gastrin concentration, which further leads to the formation of ulcer.Male Wistar or Sprague Dawley rats weighing around 200 g are selected,Administered cysteamine Hcl of dose 280 mg/kg orally three times in a day on the first day of experiment. For the treated animals: Administer the drugs twice, before 30 min of first dose and again after 24 hrs. After 48hrs of the first dose of cysteamine HCl the rats are sacrificed. The duodenal ulcers are formed 2 -4 mm away from the pylorus on the anterior wall of the duodenum and frequently perforate the liver. The intensity of the duodenal ulcers is evaluated **[39]**.

Table 2: Medicinal plants with antiulcer properties, reported phytochemicals and Suggested mechanism

Botanical name, family, common English name	Parts used	Active constituents	Screening method (model) applied	Suggested mechanism	Reference
Moringa oleifera (Family; Moringaceae) English: Drumstick	Root-bark	Alkaloids, flavonoids, proanthocyanidins cinnamates	Ethanol & pylorus ligationinduced gastric ulceration.	Increase the pH of gastric content	Choudhary *et al* **[6]**
Parkia speciosa(Family; Fabaceae) English: Bitter bean or stink bean	Leaves	Terpenoids, phenolic compounds, flavonoids	Ethanol-induced gastric mucosa injury in rats	Increase anti – oxidant defense enzymes Glutathione	Al Batran *et al* **[7]**
*Piper tuberculatum*jacq. (Family; Piperaceae) English: Black pepper	Fruits	Alkaloids, flavonoids, tannins	Ethanol induced acute lesions	Increase gastric mucus & Glutathione	Burci *et al* **[8]**
Morus alba (Family; Moraceae) English: White mulberry	Whole plant	Steroid (albosteroid), Phenolic components	Pylorus ligation & ethanol-induced ulcer models	Reduce GR & LPO	Ahmad *et al* **[9]**
Oxalis corniculata L.(Family; Oxalidaceae) Eng.: Creeping wood sorrel or Indian sorrel	Whole Plant	Glycosides, Phenolic compounds, flavonoids, tannin, phytosterols	Pylorus ligation & indomethacin-induced gastric ulceration	Antisecretory action by decreasing total gastric juice	Sakat *et al* **[10]**

Bauhinia purpurea L. **(Family; Fabaceae) English: Butterfly Tree**	**Leaves**	**Flavonoid & tannin**	**Ethanol & Indomethacin-induced gastric ulcer**	**Antiulcer, anti-secretory action attributed to its phytochemicals**	**Hisam *et al* [11]**
Momordica dioica Roxb **(Fam.; Cucurbitaceae) English: Spine gourd**	**Fruits**	**Alkaloids, fragrant extractive matter, trace manganese in ash**	**Stress and pylorus ligation-induced ulcers**	**Decrease in the level of H^+K^+ATPase**	**Vijayakumar *et al* [12]**
Terminalia belerica Roxb. **(Fam.; Combretaceae) Eng.: Beleric myrobalan**	**Fruits**	**Tannins, ellargic acid, ethyl gallate, galloyl glucose, β-sitosterol**	**Ethanol & pylorus ligation-induced ulcers**	**Increase resistance to necrotizing agents**	**Jawanjal *et al* [13]**
Acacia niloticaLinn.**(Family; Fabaceae) English:Gum Arabic tree**	**Young seed less pods**	**Phenolic components**	**Swimming stress, NSAID & Pylorus ligation induced gastric**	**Reduction of gastric acid secretion, show muco-protection**	**Bansal *et al* [14]**
Pithecellobium dulce**(Family; Fabaceae) English: Tamarind, Madras Thorn**	**Fruits**	**Glycoside like quercetrin, poly phenolic constituents, saponin**	**Chemical and stress induced ulcer models**	**Decrease H^+K^+ATPase, myeloperoxidase**	**Megala *et al* [15]**
Melastoma malabathricum Linn.**(Fam.Melastomataceae) English: Indian Rhododendron**	**Leaves**	**Flavonoids, triterpenoids & alkaloids.**	**Ethanol and Indomethacin-induced gastric ulcer**	**Decrease ulcer index in ethanol induced gastric ulcer**	**Zabidi *et al* [16]**
Calophyllum brasiliense Camb (Fam.; Calophyllaceae) English: Guanandi	**Stem bark**	**Chromanone acids**	**Ethanol & Indomethacin-induced gastric ulcer**	**Reduction of MDA and CAT levels**	**Lemos *et al* [17]**
Zingiber montanum**(Family; Zingiberaceae) English: Cassumunar ginger**	**Rhizome**	**Zerumbone, terpineol, essential oil**	**1N HCl induced gastric lesions**	**Exhibit cyto-protective effect against noxious agent**	**Al-Amin *et al* [18]**
Achyranthes aspera**(Fam. Amaranthaceae) English: Prickly chaff flower, devil's horsewhip**	**Leaves**	**Flavonoids, saponins & tannins**	**Pylorus ligation &chronic ethanol induced ulcer**	**Reduce volume of gastric juice and total acidity**	**Das AK *et al* [19]**
Musa sapientum**(Family; Musaceae) English: Banana**	**Unripe fruit**	**Polyphenols, monomeric flavonoid (leucocyanidin)**	**Indomethacin-induced ulcer**	**Antiulcer effect due to presence of flavonoid (leucocyanidin)**	**Prabha *et al* [20]**
Quassiaamara (L.)**(Fam.; Simaroubaceae) English: Amargo, Bitter-ash, Bitter-wood**	**Bark**	**Quassin& 2 meth oxycanthin-6-one, beta-sitosterol, gallic acid**	**Indomethacin-induced ulcer**	**Inhibition of histamine H^2 receptor**	**Raji *et al* [21]**
Brassica oleraceae**(Family; Brassicaceae) English: Wild cabbage**	**Leaves**	**Flavonoid, phenolic compounds**	**Acetylsalicylic acid- induced ulcer**	**Inhibit the gastric damage**	**Carvalho *et al* [22]**
Rhizophora mangle L.**(Fam.; Rhizophoraceae) English: Red mangrove**	**Bark**	**Flavonoids, quercetin glycoside, tannins**	**Acetylsalicylic acid- induced ulcer**	**Upregulation of COX-2 & EGF, enhance PGE^2**	**de-Faria *et al* [23]**
Samanea saman (Jacq) merr **(Family; Fabaceae) English: Rain tree**	**Bark**	**Flavonoids, tannins, terpenoids & saponin**	**Ethanol and stress induced gastric lesions**	**Reduce free acidity & volume of acid secretion**	**Arumugam *et al* [24]**
Polyalthia longifolia**(Family; Annonaceae) English: Indian mast tree or Indian fir tree**	**Leaves**	**Alkaloids, tannins, saponins, glycosides**	**Ethanol and EtOH/HCl induced ulcer**	**Reduction of ulcer index**	**Chanda *et al* [25]**
Bauhinia purpurea**(Family; Fabaceae) English: Orchid tree, Camel's Foot Tree**	**Leaves**	**Saponins & sugar-free polyphenols**	**Ethanol & indomethacin induced gastric ulcer**	**Increase gastric wall mucus secretion**	**Zakaria *et al* [26]**

***Raphinus sativus Linn*(Family; Cruciferae) English:Radish, daikon, Japanese radish**	**Leaves**	**Glucosinolates, isothiocyanates, phenolic compounds**	**acetic acid & pylorus ligation induced ulcer**	**Decrease the ulcer index, total acidity and free acidity**	**Devaraj *et al* [27]**
***Passiflora foetida L.* (Fam.; Passifloraceae) English: Wild maracuja, wild water lemon**	**Whole plant**	**Glycosides, phenolic compounds, flavonoids, phytosterol**	**Ethanol & aspirin induced gastric ulcer**	**Reduce lipid peroxidation & increase glutathione**	**Sathish *et al* [28]**
***Tamarindus indica L.*(Family; Fabaceae) English: Tamarind fruit, Tamarindo**	**Seed coats**	**Glycoside like quercetin, poly phenolic constituents, saponin**	**Ibuprofen, alcohol & pylorus ligation induced gastric lesions**	**Reduce the total vol. of gastric juice, free and total acidity**	**Kalra *et al* [29]**
***Terminalia chebula Retz.* (Fam.; Combretaceae) English: Myrobalan**	**Fruit**	**Triterpenoids, tannins, Phenolic compounds, flavonoids**	**Aspirin, ethanol and cold restraint stress-induced ulcer methods**	**Reduce the total vol. of gastric juice &increase pH**	**Sharma *et al* [30]**
***Cedrus deodara.*(Family; Pinaceae) English: deodar cedar, Himalayan cedar, or deodar**	**Wood**	**Flavonoids, essential oil like α- terpineol, linalool**	**Pylorus-ligated & ethanol induced gastric lesions in rats.**	**By protecting mucosal layer of stomach from ulceration**	**Kumar *et al* [31]**
***Morindacitrifolia L.*(Family; Rubiaceae) English: Indian mulberry**	**Unripe fruits**	**Polyphenol, flavonoids, tannins, carotenoids, ascorbic acid**	**Acute gastritis induced by ethanol and serotonin, and chronic gastric ulcer induced by acetic acid**	**Suppress the development of gastric lesions**	**Mahattanadul *et al* [32]**
***Syzygiumaromaticum*(Family; Myrtaceae) English: clove**	**Flower buds**	**Volatile terpenes, phenylpropanoid, essential oil, eugenol**	**Indomethacin-induced and ethanol/HCl-induced ulcer model**	**Stimulate the synthesis of mucus**	**Santin *et al* [33]**
***Cassia fistula* (Fam; Caesalpinaceae) English: golden shower tree**	**Leaves**	**Alkaloids, tannins, phenolic compounds, glycosides**	**Pylorus ligation-induced gastric ulcer**	**Strengthening of mucosal defense mechanism**	**Karthikeyan *et al* [34]**
***Apium graveolens L*(Family; Apiaceae) English: Celery**	**Whole plant**	**Flavonoids, vitamin A, B, C, fibers, mineral matters, calcium, phosphorous, iron**	**Indomethacin cytodestructive agents (80% ethanol, 0.2 M NaOH and 25% NaCl) and cold restraint stress induced ulcer model**	**Replenish the depleted levels of GWM and gastric mucosal NP-SH**	**Al-Howiriny *et al* [35]**
***Hedyotispuberula*(Family; Rubiaceae) English: Indian madder**	**Whole plant**	**Alkaloid, tannin, terpenoid, saponins, phenol, xanthoprotein**	**Indomethacin (IND), ethanol & pyloric ligation (PL)-induced gastric ulcer models in rats.**	**By increasing pH&decrease vol., acidity and pepsin content of gastric secretion**	**Joseph *et al* [37]**
***Momordica charantia L.*(Family;Cucurbitaceae) English: 'Bitter gourd'**	**Fruits**	**Steroids, triterpinoids, reducing sugars, alkaloids, phenolic compounds, flavonoids, tannins**	**Acetic acid, pylorus ligation, ethanol induced chronic gastric ulcer**	**Increase in gastric mucosal contents**	**Alam *et al* [38]**

ESTIMATION OF PARAMETERS: [39]

Estimation of free radical generation: Homogenization (5%) in ice cold 0.9% saline is done to the fundic part of the stomach with a glass homogenizer for 30

second. The homogenate is further centrifuged at 800× g for 10 min, followed by centrifugation of the supernatant at 12000×g for 15 min. Mitochondrial fraction is obtained which is used for the following estimation. Statistical analysis is done by student's t-test.

Lipid peroxides (LPO): LPO product malondialdehyde (MDA) is estimated using1,1,3,3-tetraethoxypropane as the standard and is presented as n mol/mg protein.

Super oxide dismutase (SOD) activity: Inhibition of reduction of nitro blue tetrazolium (NBT) to blue colored Formosan in presence of NADH and phenazine methasulphate (PMS) is measured using n-butanol as blank at 560 nm. One unit of enzyme activity is expressed as the amount of enzyme that inhibits rate of reaction by 50% in one min under the define assay condition and the results are expressed as unit (U) of SOD activity/mg protein.

Total protein: Lowry method was adopted for the estimation of total protein. To 0.1 ml of the tissue homogenate, 0.9 ml of water, 4.5 ml of alkaline copper sulphate reagent are added and allowed to stand in the room temperature for 10 min. To the above mixture, 0.5 ml of Folin's reagent is added. After 20 min, the blue color developed, measured at 640 nm. The level of protein present is expressed as mg/g tissue or mg/dl

Estimation of free acidity and total acidity: The content of gastric juice is centrifuged at 1000rpm for 10 mins.1 ml of supernant liquid is Pipette out and diluted to 10ml of distilled water. P^H of the solution is noted with the help of p^H meter. Titrate the solution against 0.01N NaOH solution using topfers reagent as an indicator. Titrate to end point till the solution turns to orange colour. Note the quantity of NaOH corresponding to free acidity. Titrate further till the solution gets back its pink colour by using indicator phenolphthalein. Note the total volume of NaOH, this represents total acidity. It can be expressed as mEq/l/100g. Following formula is used to calculate acidity:

$$\text{Acidity} = \frac{\text{Volume of NaOH} \times \text{Normality}}{0.1} \times 100 \text{ mEq/l/100g}$$

Ulcer Score, Ulcer Index and % Inhibition: After rats are sacrificed, the stomach of a rat is opened along the greater curvature, washed slowly under running tap water, put on the slide and observe under 10X magnification for ulcer. Score of ulcers is determined as: 0 = Normal coloured stomach, 0.5 = Red colouration, 1 = Spot ulcers, 1.5 = Haemorrhagic streaks, 2 = Ulcers ≥ 3 but ≤ 5, 3 = Ulcers > 5

The mean ulcer score for each animal is described as Ulcer index. The formula for ulcer index is as follows:

$UI = UN + US + UP \times 10^{-1}$

Where UI = Ulcer index, US = Average number of severity score in animals, UN = Average number of ulcers as per animal, UP = Percentage of animals with ulcers.

Percentage of ulcer inhibition is calculated as:

$$\% \text{ Inhibition of ulcer} = \frac{\text{Ulcer index control} - \text{Ulcer Index test}}{\text{Ulcer index control}} \times 100$$

Histological studies: Gastric tissue samples from each group are fixed in 10% formalin for 24 h and are embedded in paraffin and section (3-5μm) and stained with haematoxylin and eosin dye. The histochemical sections are evaluated by light microscopy.

SUMMARY AND CONCLUSION

The main objective for doing this review is to present an overview of antiulcer models, evaluating parameters, treatment with herbal drugs. Pathophysiology of peptic ulcer remains unexplained, Current pharmacological management of gastric ulceration is directed to the reduction or neutralization of gastric acid secretion. Despite of various treatment measures traditional medicine remains the efficient method to treat peptic ulceration. The various methods suggested in this review meets the established criteria for a useful experimental ulcer model and thus represents a viable research tool.

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