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Nanosuspension of Quercetin and Kaempferol Ameliorates/Attenuates Rifampicin-Isoniazid Induced Hepatocellular Damage in SD Rats

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KEYWORDS
Quercetin, kaempferol, hepatic cells damage, antioxidants, free radical

ABSTRACT:
Flavonoids are potent antioxidants used for hepatoprotective activity. Quercetin and Kaempferol are widely studied for free radical scavenging activity. The aim of the present study was to develop nanosuspension of quercetin and kaempferol and evaluated its hepatoprotective activity against antitubercular drugs isoniazid and refampicin induced hepatic damage in SD rats. SD rats were used in my research study. In the research study hepatic cell injury was induced due to the administration of isoniazid and rifampicin (100mg/kg) for 21 days in combined form. Quercetin and kaempferol were administered with a dose of 50mg/kg. At the end of the study blood was collected by retro-orbital puncture, and liver was quickly removed under ketamine anesthetics. Quercetin and kaempferol (50mg/kg) caused restoration of biochemical enzymes like AST, ALT, ALP, total bilirubin etc, and also showed normal histology of hepatic tissues. The outcome of the study proved that the nanosuspension of quercetin and kaempferol could potentially to treat hepatocellular damage in SD rats. It's also has free radical scavenging activity.

Introduction

The largest organ in the body is the liver which regulates homeostasis. The liver is involved in nearly all processes related to metabolism linked to growth, immunity, disease prevention, dietary requirements, creation of energy, and procreation. [1, 2] Some of the primary causes of hepatotoxicity are drug-induced liver damage [3]. Hepatotoxicity is described as any damage or impairment to the liver tissues induced by a medicine, chemical, or other substance. [4] When medications are used for a prolonged period of time, a contradiction among pro-oxidant agents and antioxidants is noticed, [5] Its kind of stress is often responsible for fibrosis, inflammatory condition, and hepatitis. [6] Isoniazid combined with Rifampicin are significant medications used to treat tuberculosis caused by Mycobacterium tuberculosis [7]. Tuberculosis (TB) is an airborne transmissible disease that is yet one of the world's biggest public health challenges nowadays. [8] On annual basis, millions of person suffer from tuberculosis, and around 2 million loses their lives [9]. The first line of antitubercular drugs are rifampicin and isoniazid (in combination), however, liver toxicity associated with their usage remains to be a major clinical concern and pathogeneses like fibrosis, inflammation, and cirrhosis are usually triggered by this kind of stress. [10, 11] Isoniazid, an isonicotinic acid hydrazide, is extremely cytotoxic toward replicating tubercle bacilli. N-acetyltransferase and amidohydrolase directly or indirectly metabolize INH to acetyl hydrazine and hydrazine [12]. CYPs may oxidize acetyl hydrazine and hydrazine in order to produce hepatotoxic intermediates [12]. CYP2E1 has been implicated in INH-related hepatotoxicity in human genetic research investigations [13]. Rifampicin, is a powerful antimicrobial that reduces the production of RNA in an extensive broad range of pathogenic microorganisms. Isoniazid is used to kill the bacterial cell wall and sterilize mycobacterium tuberculosis in cellular as well as outside of the cell variables. Rifampicin has been found to be a potent stimulant of oxidase enzyme with several functions, which leads to isoniazid liver toxicity [14]. Rifampin, could generate inflammatory mediators

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and boost cytokine-induced nitric oxide and Interlukin-8 production inside an epithelium line of cells from hepatic cells [15]. Different types of CYPs, including CYP2E1, CYP1A1, and CYP1A2. RFP has been involved in the process of free radical generation, and variations in CYP overexpression may be connected to rifampicin-mediated free radical production. According to previously researched data, it has been found that antitubercular drugs caused oxidation in hepatic tissues that lead to liver toxicity in individuals [16]. Over a long period of time ingestion of these types of agents is associated with so many ADRs such as liver damage, cardiotoxicity, renal toxicity, etc. Advent in nanotechnology has arrived in drug delivery technologies. The use of nanotechnology makes it possible a more targeted approach as well as improved bioavailability. This technology is appropriate in hydrophobic as well as hydrophilic nature. The drug delivery systems nanoformulation based are a prominent method to optimize the pharmacokinetic characteristics of medicinal compounds. There are so many nanoformulation available like liposomes, polymeric nanoparticles, nanoemulsion nanosuspension, dendrimers etc [1-5]. The nanosuspension technique is one of the most successful methods for enhancing solubility. Drugs can also be released gradually by nanosuspension. [7]

Isoniazid induced liver tissue damage (Molecular mechanism)

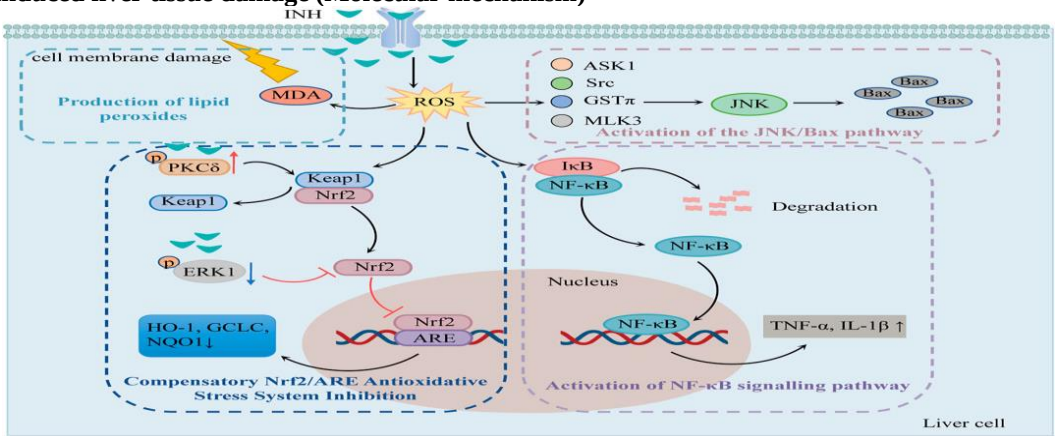

Fig 1 Isoniazid induced liver damage

Isoniazid induced liver damage is commonly related to the creation of Oxygen compounds that are extremely responsive, which function like trigger the peroxidation of fatty substances as well known component of cell membrane degeneration and impairs the function of liver tissues. [17]. As shown in Fig.1we know, organisms have two antioxidant defense frameworks: one enzymatic, which includes superoxide dismutase, glutathione peroxidase, catalase, and others, and non-enzymatic, which includes low glutathione and metallothionein are two examples on low-molecular-weight molecules that reduce the regulation of reactive oxygen species levels by scavenging radical substances produced. Isoniazid is known to cause cholestasis via raising bile acid retention and mitochondrial damage. [18]. Furthermore, INH and RFP-induced hepatotoxicity have been linked to changes in numerous cellular defence systems [19]. Metallothionein is an inducible, cytosolic protein with a low molecular weight and a high cysteine component as approximately 33%. Metallothionein are devided into 4 class (isoform) like as metallothionein-I, metallothionein-II, metallothionein-III, and metallothionein-IV. Metallothionein -I and metallothionein -II are identified in every single tissue, but metallothionein -III and metallothionein -IV are found mostly in the central nervous system and squamous epithelia [20]. Many physiological systems rely on metallothionein, like homeostasis, protection against toxic substances and oxidative decay, immunological consequence, regulate metabolic processes, carbon capture properties, and storage. [21-22]. Currently, Metallothionein has been recommended as an antioxidant because of its elevated concentration of sulfhydryl. [23], [24].

As a kind of flavonoid, kaempferol fig. 2(3,40,5,7-tetrahydroxyflavone) is found in many therapeutic plants, vegetables, and fruits. Kaempferol-containing plants have been proposed as a healthy multifunctional diet with hepatoprotective effects. In vitro and in vivo, kaempferol has been proven to be a precursor and inhibitor of CYP2E1 expression, as well as having anti-oxidant, anti-inflammatory, and immunomodulatory activities. Kaempferol has recently been employed as an adjuvant preventing CYP2E1-mediated hepatotoxicity caused by medications like INH and RIF [25]. In addition, kaempferol's phenolic ring and hydroxyl groups may give a hydrogen atom to free

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radicals and the expanded linked chemically aromatic system that can delocalize an electron that is not paired. [26].

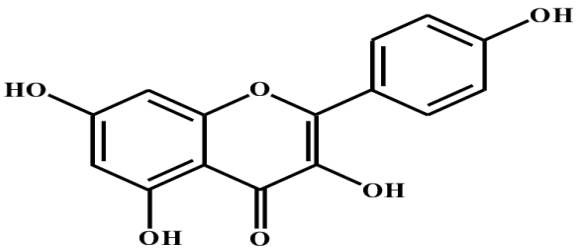

Fig 2 Structure of kaempferol

Quercetin (flavonoid) fig.3 is found in a variety of veggies and fruits such as grapes, apples, blueberries, and onions [27,28]. Quercetin has been shown to have biological, pharmacological, and therapeutic effects that are thought to be derived from its antioxidant capacity, and it can reduce ethanol-induced mitochondrial damage [15],[16]. Many pre-clinical research has confirmed that quercetin has hepatoprotective, antiviral, antioxidant anti-inflammatory, cardioprotective, anticancer, and neuroprotective characteristics, etc. [29-39]. The qualities of quercetin have led to its acceptance as a possible therapy for inflammatory illnesses, cancer, and related problems such as cachexia [34, 38, 40, 41]. However, there is still some ambiguity about quercetin's possible toxicity, which makes its use in the clinic difficult. [30, 42–47].

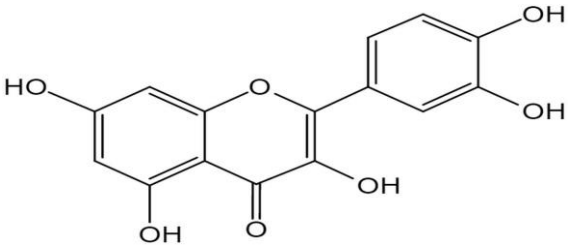

Fig 3 structure of quercetin

Materials and methods

Sylimarin, quercetin, and kaempferol were bought from Sigma-aldrich, and sylimarin got a gift sample, and isoniazid, rifampicin, PEG 400, and tween 80 were purchased from SD fine chem. The nanosuspension of Quercetin and kaempferol were prepared from the Antisolvent precipitation method. In this method taken Quercetin & Kaempferol (50mg/ml), Polymer PEG & SurfactantTween 80, at a fixed flow rate (8ml/min) done Magnetic stirring (800 to 1000rpm). At a fixed flow rate, the drug solution was quickly injected into the antisolvent (deionized water and Surfactant) of definite volume under magnetic stirring.

Characterization of Prepared Nanosuspension

Morphology-

The morphological evaluation of prepared nanosuspension was conducted by using Transmission electron microscopy (TEM from Zamia Hamdard)

- **Zeta Potential-** The mean particle size and zeta potential of prepared nanosuspension of quercetin and kaempferol was carried out via Jamia Hamdard University, Delhi (Malvern Panalytical Ltd. Instrument serial no. MAL1278078) Fig – shown particle size and zeta potential of prepared nanosuspension.

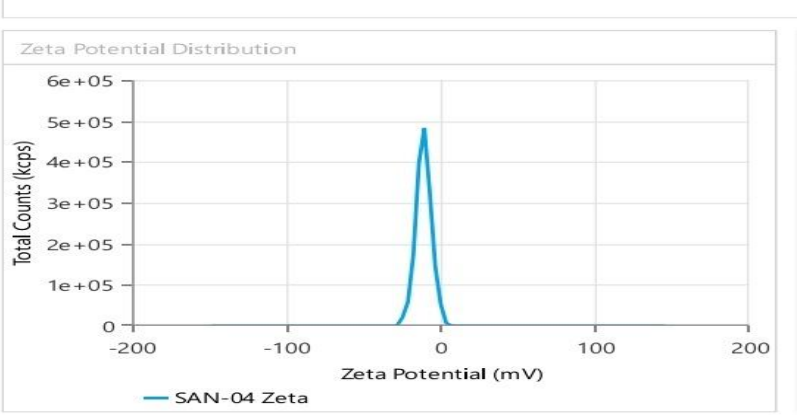

Fig 4 Zeta potential of nanosuspension of Q&K

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TEM (Transmission Electron Microscopy)- It had been carried out through AIIMS Delhi and the result is within a nanosize range. Fig shows TEM of prepared nanosuspension.

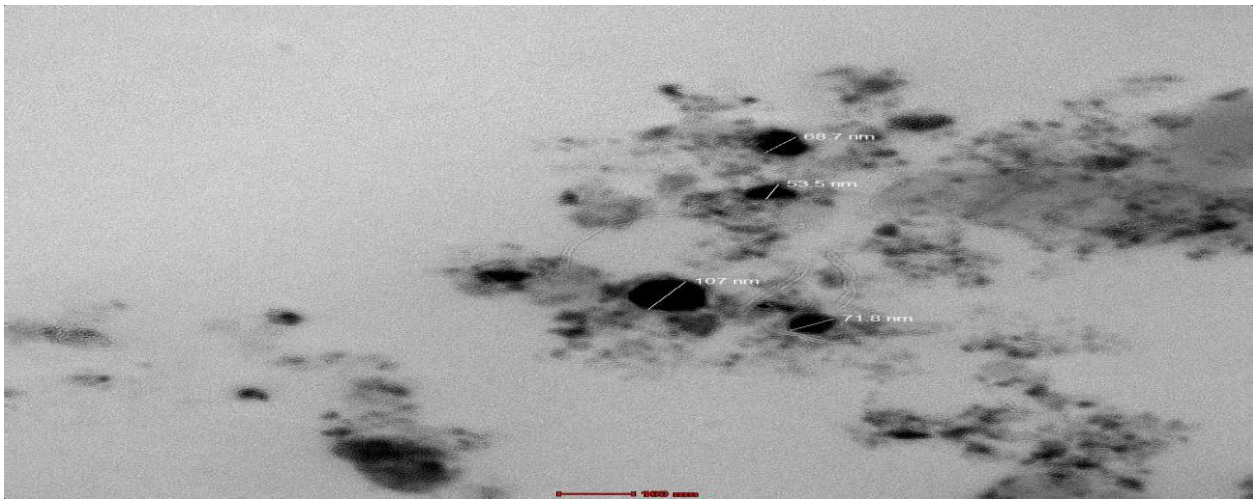

Fig 5 TEM of nanosuspension of Q&K

Experimental Animals-

Male/female Sprague Dawley rats with a weight range (100-150 g) were obtained from the Central Drug Research Institute (CDRI) in Lucknow and housed at the Integral University Lucknow departmental animal house for this study. All rats were taken care of individually in cages made of polypropylene five each in a separate cage) according to typical laboratory atmospheres (12 hr daylight and twelve hours of dark during day and night cycle), and the rat's house thermostat had maintained at 22± 3°C, and the humidity ratio was kept at (50 ±15%). The rats were provided with a suitable diet and given water ad libitum. The experiments have been carried out in compliance with the CPCSEA guidelines, and granted ethical approval from the IEAC of the Faculty of Pharmacy, Integral University Kursi Road Lucknow (Approval No. IU/IAEC/21/07).

Experimental Design- After 7 days acclimatization, the animals were put into five groups of five rats in each group. [48] The study's treatment regimen is as follows:

Table no.1.

Groups (n=5)	No. of Animal	Dosage, Route of administration, & duration
1.Normal control	5	1% (CMC1ml /kg, p.o.) for 21days.
2.Hepatotoxic group	5	Isoniazid (100mg/kg/po)+ Rifampicin(100mg/kg/po) for 21 days.49
3.Standard group	5	Sylimarin (100mg/kg/po) + Isoniazid (100mg/kg/po) + Rifampicin (100mg/kg/po) for 21 days .
4.TreatmentI (Conventional)	5	Quercetin(50mg/kg/po) + Kaempferol(50mg/kg/po) + Isoniazid (100mg/kg/po) + Rifampicin (100mg/kg/po) for 21 days.
5. Treatment II (Nanosuspension)	5	Quercetin Nanosuspension (50mg/kg/po) + Kaempferol Nanosuspension (50mg/kg/po) + Isoniazid (100mg/kg/po) + Rifampicin (100mg/kg/po) for 21 days.

Blood samples were taken by heart puncture into uncontaminated transparent plastic tubes under ether anesthesia after 24 hours following the conclusion of the treatment period (i.e. day 21). For further analytical studies, the samples were segregated by centrifugation (cool) and placed it at maintained 20°C. The sample was tested for alanine transaminase, [50], aspartate transaminase [51], alkaline phosphatase [52], TP[53], Alb[54], and bilirubin [55]. The animals were euthanized by cervical dislocation immediately after blood collection, and their liver were quickly removed.[56]

Histopathological Evaluation-

To preserve the liver, it was kept in a formalin soln (10%). In the laboratory, paraffin wax was used to mount the tissue, and slices were cut for further histological evaluation.

Statistical Analysis-

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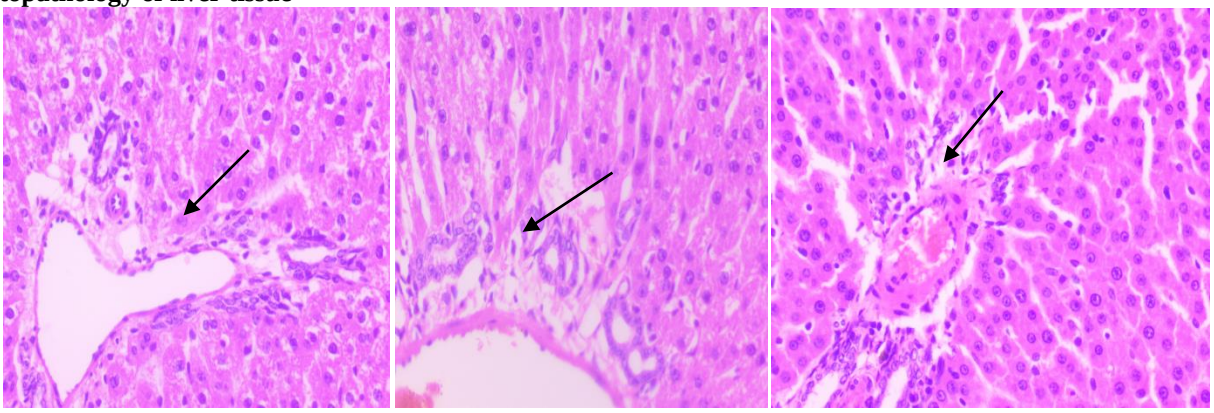
The details were provided as the average standard error of the mean (mean±SEM). Student 't'- test was followed by an individual comparison utilizing the Newman-Keuls test with the help of graph pad prism software to determine the degree of significance. Less than 5% ($p<0.05$) probability value have considered and taken to be statistically prominant. [57]

Table 2-Statistical data of treatment

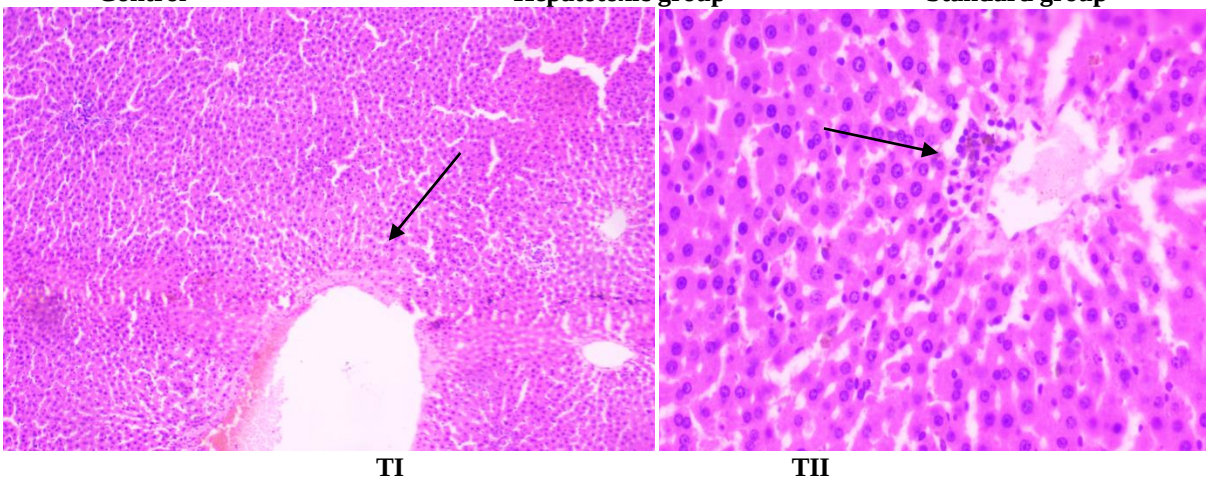
Liver specific variables	Group I (Normal control)	Group II (Toxic)	GroupIII (Std)	Group IV (Q&K Conventional)	Group V (Q&K Nanosuspension)
SGOT	112.2±1.30	158.20±5.63 (a)	115.4±1.14 (b)	126.6±2.40 (c)	118±7.50 (c,d)
SGPT	103±1.10	132.20±3.63 (a)	107.2±1.39 (b)	116.8±3.03 (c)	112±2.70 (c,d)
Bilirubin Total	0.93±0.008	1.68±0.57 (a)	0.94±0.011 (b)	1.08±2.77 (c)	0.97±0.015 (c,d)
Alkaline Phosphatase	184.4±1.40	818±32.90 (a)	191.8±1.48 (b)	270.8±2.07 (c)	193.6±2.07(c,d)

a- Group $p<0.05$ significantly distinct with the normal control
b- Group $p<0.05$ significantly distinct with toxic group
c- Group $p<0.05$ significantly distinct with silymarin treated group
d- Group $p<0.05$ significantly distinct with Quercetin and kaempferol conventional treated

Histopathology of liver tissue



Control **Hepatotoxic group** **Standard group**



TI **TII**

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- **Control-** Showed normal histology in liver tissues and normal hepatic lobules.
- **Hepatotoxic-** Showed lymphocytic infiltration. There is moderate sinusoidal dilatation along with focal hepatocytic degeneration seen.
- **Standard Group-** Showed almost normal histology except mild focal periportal lymphocytic infiltration.
- **TI(Q&K Conventional)-** Showed mild focal hepatocytic degeneration along with infiltration.
- **TII (Q&K Nanosuspension)- -** Showed almost normal histology as compared with control and standard.

Discussion-

Because toxic compounds have a substantial influence on the liver, liver marker enzymes are extremely sensitive markers of toxic levels and be particularly helpful in the evaluation of hepatic damage. The most often used biochemical markers to detect hepatic damage, its function depends on alanine transaminase, aspartate transaminase, alkaline phosphatase, and serum bilirubin. In this study, quercetin combined dosing decreased high blood enzyme indicators

including alanine transaminase, aspartate transaminase, alkaline phosphatase, as well as bilirubin levels.[54] The restoration of enzyme levels of quercetin and kaempferol treatment suggested that quercetin and kaempferol have marked hepatoprotective activity and may also preserve the proper shape and size of the cell membrane of liver, also cut the leakage of hepatic enzymes in the bloodstream. Isoniazid and rifampicin is also caused injury in hepatic tissue/cells, so heal its properly with quercetin and kaempferol

Conclusion

According to the findings of this investigation, quercetin and kaempferol show hepatoprotective action. These findings lead us to believe that quercetin and kaempferol might provide a novel method for treating Isoniazid and kaempferol induced liver damage.

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Conflict of interest

The authors declare no conflict of interest to this article.

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