In the present study, the protective effects of NAC, naringenin, vanillin and carvedilol were investigated on several parameters related to paracetamol-induced hepatotoxicity in rats. Hepatotoxicity was induced by a single oral dose of paracetamol (1 g/kg). All drugs were given for 7 successive days before paracetamol-administration. The effects of the tested drugs on hepatotoxicity markers including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and gamma-glutamyl transferase (GGT) activities as well as serum total protein (TP) level were estimated. Also their effects on oxidative and nitrosative stress markers including hepatic malondialdehyde (MDA), reduced glutathione (GSH), catalase and total nitrate/nitrite (NOx) contents or activity were assessed. In addition, the effects of the tested drugs on serum tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) levels were also determined as inflammatory markers. Histopathological examination of liver tissues was also done. Moreover, immunohistochemical study and western blot analysis were done for estimation of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expression levels in liver tissues. Furthermore, the effects of the test drugs on the relative liver weight were determined.

The main findings of the current study could be summarized as follows:

1. Paracetamol-induced hepatotoxicity significantly elevated serum ALT, AST, LDH and GGT activities and significantly decreased serum TP level.
2. N-acetyl cysteine significantly decreased serum ALT, AST, LDH and GGT activities while it did not significantly affect serum TP level of hepatotoxic rats.

3. Naringenin significantly reduced serum ALT, AST, LDH and GGT activities and significantly elevated serum TP level.
4. Vanillin significantly decreased serum ALT, AST and GGT activities and significantly increased serum TP level. It did not significantly affect serum LDH activity of hepatotoxic rats.
5. Carvedilol significantly decreased serum ALT and AST activities and significantly increased serum TP level. It did not significantly change serum LDH and GGT activities of hepatotoxic rats.
6. Paracetamol-induced hepatotoxicity significantly increased hepatic MDA, catalase and NOx contents or activity while it significantly decreased hepatic GSH content.
7. N-acetyl cysteine significantly decreased hepatic MDA content while it significantly increased hepatic GSH and NOx contents.
8. Naringenin significantly decreased hepatic MDA content and catalase activity while it significantly increased hepatic GSH content. It did not significantly affect hepatic NOx content of hepatotoxic rats.
9. Vanillin significantly reduced hepatic MDA content and catalase activity while it significantly increased hepatic GSH and NOx contents.
10. Carvedilol significantly reduced hepatic MDA content and catalase activity while it did not significantly change hepatic GSH and NOx contents of hepatotoxic rats.
11. Neither paracetamol nor the test drugs significantly affect the relative liver weight.
12. Paracetamol-induced hepatotoxicity resulted in significant elevation of serum TNF-α and IL-1β levels.

13. N-acetyl cysteine, naringenin, vanillin and carvedilol significantly decreased paracetamol-induced elevation of serum TNF-α and IL-1β levels.

14. Induction of hepatotoxicity by paracetamol significantly increased hepatic iNOS and COX-2 expressions.

15. N-acetyl cysteine, naringenin, vanillin and carvedilol significantly reduced hepatic iNOS and COX-2 expressions.

16. Western blot analysis of liver tissues of paracetamol-treated rats revealed significant increase in hepatic iNOS and COX-2 expression levels compared to normal control group.

17. N-acetyl cysteine, naringenin, vanillin and carvedilol reduced paracetamol-induced elevation in hepatic iNOS and COX-2 expression levels.

18. Histopathological examination of liver tissues of paracetamol-treated rats showed severe hepatic damage manifested by moderate vascular congestion of central vein and hepatic sinusoids, moderate inflammatory changes, inflammatory cell infiltration, fatty degeneration of hepatocytes, centrilobular necrosis and hyperplasia of Kupffer cells.

19. Histopathological examination of liver tissues of rats treated with NAC, naringenin, vanillin and carvedilol showed mild hepatic changes than those observed in paracetamol group indicating that they began to restore the normal appearance and physiological state of liver tissues.

According to the previous findings, it could be concluded that:

- Paracetamol-induced hepatotoxicity resulted in hepatic dysfunction and a state of oxidative stress.

- Paracetamol also induces inflammation as evidenced by increased serum levels of TNF-α and IL-1β as well as hepatic iNOS and COX-2 expressions.
- In addition, hepatic cellular injury and inflammatory changes were observed in liver tissues.
- Prophylactic administration of NAC, naringenin, vanillin and carvedilol to hepatotoxic rats attenuated most of the biochemical, histopathological and immunohistochemical changes induced in rats by paracetamol.
- The most likely proposed mechanism for the observed effects of the test drugs is probably related to their antioxidant properties.
- In addition, these drugs also possess anti-inflammatory properties due to their ability to suppress NF-κB activation and inhibit paracetamol-induced elevation of iNOS and COX-2 expressions.
- Naringenin, vanillin and carvedilol could be promising protective agents for clinical use against paracetamol-induced hepatotoxicity.
- Further clinical studies are required to support the previous findings.