Simulated screening of flavonoids as probable anti-*Helicobacter pylori* drug

Kashi Prakash-Gupta Rajesh · Hanumanthappa Manjunatha · Basavapattana Rudresh Bharath

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**Abstract** *Helicobacter pylori* is a major causative factor during severe gastrointestinal disorders which leads to gastric ulcer in turn gastric cancer. Discovery of drugs to control *H. pyloris* is a difficult task in view of drug resistance developed by the bacterium against continuous exposure to modern drugs. The virtual screening is an important tool which cut down the man power, cost and time by aiming at more toward target lead identification. It involves an in silico approach which enables to predict favorable protein-ligand interactions with reasonable accuracy and speed. In this perspective, virtual screening of a set of 51 flavonoid molecules for the inhibition of a key metabolic enzyme peptide deformylase (PDF) was carried out. Nobiletin, silybin, and vitexicarpin have revealed the lowest binding energy of $-10.65$, $-11.46$, and $-10.37$ KJ mol$^{-1}$, respectively, which indicates high binding affinity with target protein and identified as anti-*H. pylori* molecules.

**Keywords** *Helicobacter pylori* · Computational modeling · Molecular docking · Peptide deformylase

**Introduction**

*Helicobacter pylori* (*Hp*), a gram-negative, microaerophilic, spiral-shaped bacterium that chronically infects over a billion people worldwide (Suzuki et al., 2007; Brooks et al., 1995; Martinon et al., 2000), which was linked with gastritis and gastro-duodenal ulcers in spite of 25 years of antimicrobial intervention (Marshall and Warren, 1984; Uemura et al., 2001). There is no effective therapy for eradicating *Hp* infection, otherwise combination therapies employing one proton pump inhibitor (e.g., omeprazole) and two or three antibiotics (e.g., amoxicillin, clarithromycin, or tetracycline) have been preferred for treatment (Ulmer et al., 2003). The multiple therapies are not very effective in a clinical setting as this may develop resistance (Cameron et al., 2004). In addition, this may disrupt the natural population of commensal microorganisms in the gastrointestinal tract, potentially leading to undesired side effects. Thus, there is a need to search for an indigenous herbal or herbal based modified drugs with minimal side effects for the elimination of *Hp* which would have a major impact on present and future of the world population (Mohammed et al., 2006).

Traditional method of drug discovery has seven steps (Fig. 1), disease selection, target hypothesis, lead compound identification (screening), lead optimization, pre-clinical trial, clinical trial, and pharmacogenomics optimization. These steps were carried out sequentially (Augen, 2002), if one of the steps gets slow, it slows down the entire route. High-throughput drug screening (HTS) is time consuming (~15 years), expensive (~$800 millions), and very risky process in contrary to High-throughput virtual screening since it provides the base for integrated hit and lead optimization strategies.

The quest for new chemical entities and novel structural scaffolds is always at the heart of pharmaceutical chemistry. Virtual screening (VS) method has emerged as an adaptive response to massive high-throughput screening technologies. They are playing an increasingly larger role in drug discovery and development to discriminate putative
Potential in vitro antioxidant and protective effects of Mesua ferrea Linn. bark extracts on induced oxidative damage

K.P. Rajesh², H. Manjunatha²*, V. Krishna³, B.E. Kumara Swamy³

² Department of PC Studies and Research in Biotechnology and Bioinformatics, Jnanasahyadri, Kuvenmp University, Shankaraghatta 577451, Shivamogga, Karnataka, India
³ Department of PC Studies and Research in Industrial Chemistry, Jnanasahyadri, Kuvenmp University, Shankaraghatta 577451, Shivamogga, Karnataka, India

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A B S T R A C T
Free radicals and activated oxygen radical species are generated as a result of aerobic metabolism imbalance, if any in the antioxidant defense system against free radicals can degrade biomolecules inside the living system. In this present study, antioxidant arbitrated protective activity of Mesua ferrea L. is reported on induced oxidative damage in erythrocytes. Hb and DNA. Both, MCE (Mesua ferrea chloroform extract) and MEE (Mesua ferrea ethanol extract) exhibited significant antioxidant activity while MEE showed >90% protection to erythrocytes, Hb and DNA by virtue of high total phenolics (1.005 ± 0.005 mg EGA/mg) and total flavonoids (514.8 ± 7 mg/g) whereas MCE showed <90% but >70% antioxidant protective activity probably due to 0.596 ± 0.002 mg EGA/mg total phenolics and 275.9 ± 5 mg/g total flavonoid content. It indicates that Mesua ferrea Linn. possesses significant protective activity against induced oxidative stress by acting as a strong antioxidant and potential electro-catalyst during the electrochemical oxidation of H₂O₂. Furthermore, HPLC of MCE and MEE revealed well known various good antioxidant molecules such as gallic acid, ellagic acid, coumaric acid, vanillic acid, rutin, quercetin, myricetin and kaempferol. Thus, Mesua ferrea Linn. bark was found to be having a good antioxidant property.

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1. Introduction
Aerobic metabolic pathways in the human body normally generate reactive oxygen species (ROS) and free radicals. Aerobic organisms have developed their own efficient enzymatic and non-enzymatic self-defensive network during the course of evolution against oxidative stress to maintain cellular homeostasis (Halliwell and Gutteridge, 2007). If the array of these defensive networks becomes unable to maintain cellular homeostasis under some circumstances, the exogenous supply of antioxidants is obligatory to restore the homeostasis. This reactive species, if produced in excess, extensively cause the oxidative damage to the cellular biomolecules (Droge, 2002) and eventually contribute to the pathogenesis of numerous oxidative stress related diseases including cancer, aging, heart failure, diabetes, lung disease, neurodegenerative disorders and rheumatoid arthritis, etc. (Halliwell and Gutteridge, 2007). The antioxidants play a crucial role in scavenging the active free radicals before they attack biologically vital molecules by donating hydrogen atom to maintain the cellular homeostasis.

Generally, erythrocytes have been used as a cellular model to investigate oxidative damage, because they are considered as prime targets for free radical attack owing to the presence of both high membrane concentration of polyunsaturated fatty acids (PUFA) and the redox active protein hemoglobin (Hb), which is the potent promoter of ROS (Sadrazadeh et al., 1984; Sukalski et al., 1997). These erythrocytes undergo hemolysis and change in their shape when they get exposed to harsh conditions of H₂O₂, which indicates the oxidative damage on the erythrocytes.

Bio-molecules are vulnerable to exorbitant oxidative stress condition in vivo. Therefore Hb experiences irreversible structural changes involving iron/heme oxidation, heme-actuct products formation and amino acid oxidation when induced by H₂O₂ (Vallellan et al., 2008) which further results in the formation of potentially toxic oxidized iron species, as well as heme and protein radical(s).

Numerous synthetic and natural compounds have been reported to possess antioxidant property, but only limited number of compounds were accepted and mentioned in the list of GRAS (generally regarded as safe), as the synthetic molecules have the potential to cause serious adverse side effects. In this context, natural antioxidants have become one of the major areas of scientific research. The plant kingdom offers a wide range of medicinal plants.