

Single and Repeated Dose Effects of Phytochemicals in Rodent Behavioural Models

Vikas Kumar^{1*} and Shyam Sunder Chatterjee²

¹Department of Pharmaceutics, Banaras Hindu University, India

²Retired head of pharmacology research laboratories, Dr. Willmar Schwabe GmbH & Co. KG, Germany

***Corresponding Author:** Vikas Kumar, Department of Pharmaceutics, Neuropharmacology Research Laboratory, Indian Institute of Technology, Banaras Hindu University, Varanasi-221 005, India.

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The common co-morbid psychiatric conditions like depression, anxiety, sleep disturbances and other mental health problems have always been treated with herbal remedies since ancient times [1,2]. Ayurveda is one of the oldest known holistic health care systems recommending diverse medicinal uses of edible and other plant derived products for prevention and cure of mental illnesses commonly associated with almost all chronic medical conditions [3]. Currently available information on medicinal phyto-chemistry and pharmacology of numerous traditionally known herbal remedies are now widely used also for drug discovery purposes. Although experimental strategies and models often used for such purposes are rarely based on holistic therapeutic principles of Ayurvedic and other traditionally known systems of medicine and health care [4], there are now considerable preclinical as well as clinical evidences justifying traditionally known medicinal uses of diverse types of herbal extracts for prevention and cure of mental health problems [2,5]. It is now well recognized also that numerous phytochemicals commonly consumed with such extracts alter the functions of adaptive cellular stress pathways [6-8], and that numerous traditionally known herbal remedies possess adaptogenic properties [9-11]. However, many questions concerning their bioactive principles and their appropriate combinations and daily oral doses and treatment regimen necessary for obtaining health benefits still remain unanswered [2,12,13].

More recent efforts made in our laboratories and elsewhere to identify bioactive constituents or modes of actions on several currently commercialized psychoactive herbal remedies have not only reconfirmed that many of them possess broad spectrums therapeutically interesting bioactivities against metabolic and/or environmental stress triggered pathologies only after their repeated daily oral doses, and that structurally and functionally diverse phytochemicals commonly consumed with every day meals and drinks could as well be involved in their stress response modulating, or adaptogenic and antidepressant and anxiolytics like, activities in rodent models [14-25]. Although the psychopharmacological activity profiles observed after acute and repeated daily doses of herbal adaptogens are always not identical [26], such is not the cases for stress response modulating effects of several (but not all) stress response regulating food phytochemicals encountered in almost all of them. A common characteristic of all such food phytochemicals identified to date is that they possess anti-microbial or bactericidal activities and they are exhaustively and fairly rapidly metabolized by gut microbiota [27-29]. Since it is now evident that alterations in gut microbial ecology influences brain functions in experimental animals and human, and that stress responses are also regulated by gut microbiota [30-36], it could as well be that alterations in gut microbial ecology caused by stress and food phytochemicals consumed with herbal remedies are involved in their modes of actions.

Although phytochemists have known since long that structurally diverse food phytochemicals are present in almost all terrestrial plants, as yet little concentrated efforts have been made to define their roles in medicinally used herbal extracts. During the course of our efforts to identify stress response modulating constituents of several edible plant extracts used in ayurvedic system of medicine as tonics

or rejuvenating therapies, we could identify numerous well known edible phytochemicals commonly consumed with food, or medicinally used as vitamins, or often considered as potential drug leads by modern drug discoverers.

Since stress response modulating effects of numerous such extracts their formulations are observed after their repeated daily oral doses, we conceived and pharmacologically validated a mouse bioassay system in which the efficacies of single and repeated daily oral doses of edible phytochemicals could be quantified. Some of the observations revealing diverse spectrums of stress response modulating efficacies of different edible phytochemicals in this bioassay have already been published [19], and manuscripts of some others are in press or under preparation. Stress response modulating oral efficacies of almost all (but not every) edible plant extracts or phytochemical tested to date could be detected after their repeated daily doses only. These observations not only point out the importance of ubiquitously present edible phytochemicals in medicinally interesting psychopharmacological activity profiles of herbal remedies, but also suggest that predictive values of observations made in rodent models after repeated daily oral doses of psychoactive herbal remedies should be much higher than those made after their acute oral doses only.

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