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Special Opinion Paper

Indian *Rauwolfia* research led to the evolution of neuropsychopharmacology & the 2000 Nobel Prize (Part I)

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There is hardly any medicine, herbal or modern, which originated in India more than a century ago and became a subject of intensive research and clinical use for more than two decades ago, in the Western world than *Rauwolfia serpentina* and some of its alkaloids[1]. It is of historical interest that Indian Research Fund Association, the predecessor of the Indian Council of Medical Research (ICMR) nearly one hundred years ago, around early 1930s, had the foresight to establish an Indigenous Drug Inquiry Unit at the School of Tropical Medicine, Calcutta (now Kolkata) under Lt. Col. R.N. Chopra, the pioneer of plant-derived drugs in the country. He motivated a large number of young scientists – chemists, pharmacologists and clinicians – to pursue this line of research[2]. Others elsewhere in the country also made commendable contributions. Thus, Siddiquis[3-6] and later Anand and Malhotra in Delhi[7], Professor B.B. Bhatia and his student R.D. Kapur in Lucknow[8-11], and later his student K.P. Bhargava (revered father of the current Director General of ICMR) and Vakil from Bombay (Mumbai) independently contributed to the field[12-15]. Their courage to use this drug in the clinical practice in an era when indigenous drugs were not generally used by the practitioners of 'modern medicine' is commendable. The publications by Vakil[12-14] and Hakim[16] attracted the attention of experts in the USA on the use of *Rauwolfia* in treatment of hypertension and mental illness. Between 1950 and 1955, Bernard Brodie, Chief Pharmacologist at the National Heart Hospital, National Institute of Health (NIH), USA and Nathan Kline, Psychiatrist and Director Research, Rockland State (Mental) Hospital, New York, aggressively pursued this research[17]. Soon, Arvid Carlsson from Sweden joined Brodie to investigate the pathogenic mechanism of action of reserpine, the most readily available alkaloid of *Rauwolfia*. Carlsson continued in this field of research on return to his country and attracted many colleagues from allied disciplines to expand the whole field and finally received the Nobel Prize for Medicine/Physiology in 2000. There were others from the USA, UK, Germany, Austria, Japan, Sweden, Denmark, Switzerland and New Zealand who added to this burgeoning field of neuropsychopharmacology. While the clinical use of reserpine (Serpasil) went into oblivion, the broad field of neuropsychopharmacology took deep roots (see Part II).

The root of the *R. serpentina* Benth (N.O Apocynaceae) has been in use in India for hundreds of years for many unrelated diseases. Vakil[15] reviewed the literature on *Rauwolfia* and reported the mention of this plant in an old Hindu manuscript (1000 BC) as well as in the works of Charaka (second century AD) under the Sanskrit name of *Sarpagandha*. Chopra *et al*[2]

provided a whole list of names for the herb *"'chota-chand'* in Hindi; *'chandra' or 'chota chand'* in Bengali; *'dhan barua' or 'dhan marua'* in Bihari; *'chandra', 'chota chand', 'karavi' or 'harkai'* in Bombay; *'harkaya'* in Marhatti; *'atalagandhi' or 'patala garuda'* in Telugu; *'chuvana avilpori'* in Malay*)* as known in different parts of the country. In Patna and Bhagalpur in Bihar it was sold as *'Pagla-ka-dawa'* (insanity herb). It was also used as a herbal medicine in Malaya and Java[2]. The authors provided a long list of unrelated diseases such as corneal opacity, bites of poisonous snakes, diarrhoea, dysentery, cholera, uterine contraction, insomnia and insanity for whose treatment it was used.

Of the 130 odd species of *Rauwolfia*, eight species grow in India. There is considerable difference in the quality and content of the therapeutic alkaloids among these, the most useful being *R. serpentina*[18].

Indian contributions

Prior to mid-1950, most of the research on *R. serpentina* and its alkaloids was carried out in India. Siddiqui and Siddiqui[3-5], Sen and Bose[19] independently isolated a variety of alkaloids from the roots of *R. serpentina*, Benth. These included ajmaline, ajmalicine, ajmalinine and serpentine and serpentinine. The former found that the alkaloids obtained from the roots of the plants obtained from Dehradun were different from those obtained from Bihar[3-6]. Two of those from Dehradun were named by them as isoajmaline and neoajmaline. The ajmaline group acts as a general depressant to the heart, respiration and central nervous system, and the serpentine group causes paralysis of respiration, depression of nerves and stimulation of the heart[3-6]. They also recorded a fall of the carotid blood pressure from 10 to 15 mm after its IV injection in the femoral vein[3]. Bhatia and Kapur[8] studied the pharmacological action of these two alkaloids. However, the maximum amount of research on the pharmacology of these alkaloids was carried out by Chopra and his associates from 1933 onwards[2,20-23].

These studies were carried out at the School of Tropical Medicine in Calcutta (Kolkata) under the Indigenous Drugs Inquiry sponsored by the Indian Research Fund Association (later named Indian Council of Medical Research: ICMR). Chopra *et al*[2] reported the well marked hypnotic and sedative effect of an alkaloid isolated from *R. serpentina* in their laboratory. They concluded, "The alkaloid has a pronounced effect on the central nervous system. The alkaloid on account of its cerebral depressant properties should prove to be a valuable sedative drug". Furthermore, "It lowers the blood pressure and if administered in proper doses should be of value as a remedy against hyperpiesis"[2]. Chopra *et al*[2] reported depression of the central nervous system (CNS) in their animals using ajmaline, the only alkaloid then available. In 1941, Chopra and Chakravarty[21] found, "neither ajmaline nor serpentine produced any sedative effect on the CNS of white rats". Bhatia and Kapur[9] reported identical findings. They found, "The action of both the alkaloids on the nervous system is one of stimulation ---------- followed by depression and paralysis of various Centres" and "Both the alkaloids produced fall in blood pressure in intact, spinal and decerebrate animals". These results of animal experiments were obviously contradictory to later human studies[8]. In a paper next year, Chopra *et al*[23] reported its probable nature. Around the same time, a series of papers were published on the sedative effect of *R. serpentina* alkaloids[16,19,22-31]. It was, however, a paper by Vakil[12] in 1949 that attracted the attention of the Western world. Some highlights of this paper are given as follows: He quoted a detailed study by Ayman[32] who on the basis of his study of over 200 reports on the successful treatment of hyperpiesia by various hypotensive remedies concluded, "Proper treatment is still unknown". Vakil[12] recorded, "As early as 1940, I had made the following allusion to the subject of *R. serpentina* treatment in cases of hypertension: "After a trial of this preparation, one finds it useful in a percentage of cases of hypertension only; ----------". "After an extensive trial of various hypotensive remedies in several thousand cases of hypertension, both in private and hospital practice, during the last ten years, I have found *R. serpentina* to be the most consistently successful member of the whole group of hypotensive remedies"[12]. In a reply to his questionnaire, 46 of 50 physicians from all over India voted for "*R. serpentina* as being the best 'hypotensive' in their experience"[12]. A detailed review by him on the subject in 1955 provided up to date information on the subject[15].

Another important paper on the subject was by Bhatia from Lucknow in 1942[7] who after employing *R. serpentina* in the treatment of cases of high blood pressure, both with and without renal damage, reported it as a useful and well tolerated hypotensive remedy. There were some other Indian physicians to report their positive experience on the subject[10,19,33-35]. On the other

hand, there were a number of others who highlighted the hypnotic, sedative, tranquilizing even antipsychotic effect of these alkaloids[25-27,30]. In 1941 Chopra and Chakravarty[21] reported, "The alkaloids ajmaline and serpentine of *R. serpentina* are medullary stimulants".

International contributions

According to Wilkins[36-39], although an ancient drug, *R. serpentina* did not receive any notice by clinicians in the USA till 1950, it was in 1952 that CIBA Laboratories (now Novartis) in Switzerland published the first complete report on the isolation of reserpine, its chemistry and pharmacology. It was introduced as the drug Serpasil for the treatment of hypertension, tachycardia and thyrotoxicosis[36,37]. Wilkins while referring to Indian paper by Bhatia[7], Gupta *et al*[25] and Roy[40] stated, "The paper which really excited my interest in *Rauwolfia* as a treatment for hypertension was that of Vakil which appeared in 1949 in the British Heart Journal"[12]. He further added, "three additional years' experience since that time, in a large number of cases, has added but little to the clinical information that had already been obtained by the Indian workers. We confirmed that *Rauwolfia* is a hypotensive agent of modest potency, with a definite bradycardic and sedative action". Wilkins published a number of papers on the subject highlighting its use for hypertension[36-39]. Reserpine thus became the drug for hypertension in the USA in 1952. Wilkins (1954)[36,37] claimed that "prior to our studies all the reports on the drug were from India". According to Lobay[41], Indian physician Vakil is considered responsible for introducing *Rauwolfia* to Western Medicine. Vakil[15] in a detailed review on the subject provided a list of publications on the hypotensive effect of serpasil from the USA [Wilkins and Judson (1953), Ford and Moyer (1953); Joiner and Kauntze (1954). Doyle and Smirk (1954), Vida (1952), Arnold (1952), Seliger (1952), Arnold and Bock (1953) Sarre (1953), Neumayer (1953), Kleinsorge and Wittig (1954), Marx (1953), Meissner (1953), Watschinger (1953), Runk (1954), Klausgraber (1953); Loffler *et al* (1953) and Goto (1954)]. To this list, one may add Dustan *et al*[42], Meilman[43] and Bein[44]. As far as the antihypertensive effect of *R. serpentine,* alkaloids was concerned, there was an unanimous opinion about it utility except for a small clinical trial by Bello and Turner[45]. Even they concluded that, "Negative results of this study are not a denial of the clinical usefulness of Rauwolfia in many patients"[45]. According to a Cochrane database systematic review 2009[46] "only four randomized clinical trials could be found to meet the inclusion criteria". The authors concluded that reserpine was effective in reducing systolic BP to the same degree as other first-line antihypertensive. The only reported serious adverse effect of the *Rauwolfia* alkaloid therapy for hypertension was the development of depression resulting in suicide in a few cases[47-54]. Healy and Savage[55] in a well-argued paper 'Reserpine Exhumed', argued that, "Despite the efforts of a number of psychiatrist to counteract the 'hysteria' (Sarwer-Foner & Ogle, 1955; Ayd, 1958; Bernstein & Kaufman, 1960), reserpine entered mythology as a drug and 'The use of reserpine fell dramatically'".

As a matter of fact, reserpine was used as a sedative and a tranquiliser and even for some patients with mental disorders as was recommended in Indian folk lore, as confirmed by Sen and Bose[19], Ray[24], Gupta *et al*[25,26], Chakravarty *et al*[30], Chopra *et al*[23], and Deb[31].

Credit for introducing reserpine for neuropsychiatric conditions to psychiatrists in the USA goes to Nathan Kline of Columbia University, New York[56]. Interestingly, he learnt about it from a New York Times report in March 1953 about an Indian Psychiatrist Hakim who had been awarded a gold medal for his paper 'Indigenous drug in the treatment of mental diseases' presented at the Sixth Gujarat and Saurastra Provincial Medical Conference[56]. On the basis of an extensive review of the literature Kline was not convinced about the effectiveness of *Rauwolfia* as a treatment for schizophrenia. He observed, "There was both clinical and experimental evidence, however, that *Rauwolfia* had marked sedative properties, there was also strong evidence that *Rauwolfia* altered psychic state, even if its effect on schizophrenia was somewhat questionable". Kline provided reference to a large number of Indian publications in support of his conclusion stated above. He then embarked on a systematic scientific investigation on a larger number of patients (243 females and 168 males, total 411). All but 5.6 per cent of the patients were diagnosed with schizophrenia. At the end of the study, he concluded "*Rauwolfia serpentina* has proved to be an effective sedative for use in mental hospitals"[56]. Moreover, "There is evidence that *Rauwolfia* will reduce anxiety and obsessive and compulsive drives, and will overcome excessive inhibition and reticence"[56]. Kline published a series of papers on the subject (Barsa and Kline 1955[57], Kline and Stanley 1955[17]). Kline received the Lasker award for his studies on the role of reserpine in the treatment of psychiatric patients.

It may be mentioned that in early 1950s, the only treatment for psychotic patients was electroconvulsive therapy and insulin shock[58]. Chlorpromazine was then introduced[59]. Therefore, there was a great demand for any alternative drug for such patients. Noce *et al*[60] in 1954 from Sacramento, California initiated their investigation on the use of Serpasil (provided by Ciba Pharmaceuticals) for schizophrenia patients in October 1953. The result of their preliminary study, in the first seven months of treatment of mentally ill was so dramatic that they decided to present their preliminary findings "to stimulate others to study reserpine in all types of mentally ill and mentally retarded patients". They reported "Seventy four mentally ill and 15 mentally retarded patients received reserpine (Serpasil) for periods ranging up to seven months. Patients have undergone a metamorphosis from raging, combative, unsociable, persons to cooperative, friendly, cheerful, sociable, relatively quiet persons who are amenable to psychotherapy and rehabilitation measures"[60] And, "we believe that in 75 per cent of mentally ill patients reserpine will substitute for and excel electroconvulsive therapy, both acute state and for maintenance"[60]. The only placebo controlled randomized parallel group study of reserpine in the treatment of anxious and depressed patients were carried out by Davies and Shepherd[61]. They reported that far from causing depression (as had often been reported in patients treated with reserpine for hypertension), reserpine appeared to have antidepressant effect. They reported, "Among the 54 patients completing the trial those treated with reserpine showed more benefit than the others"[61].

H.J. Bein from the Ciba Laboratory, Basle[45], reported, "Reserpine, a new, highly active alkaloid from *R. serpentina* Benth, shows a very marked hypnotic effect and lowers blood pressure". Wilkins and Judson[39] while summarizing their experience of using reserpine for the treatment of hypertension observed, "its action is slow it produces no serious side effects, causes sedation, well tolerated for weeks and months". R.W. Wilkins from Massachusett Memorial Hospital, Boston, while primarily reporting on their experience with treatment of hypertensive patients observed some neuropsychiatric features. In addition to sedation, his patients besides control of blood pressure reported symptomatic improvement. He reported, "Many patients have become positively lyrical about their sense of well-being". Statements such as "I have never felt as well" or "I haven't felt this good for years", "This is how I dreamed of feelings", "Nothing bothers me anymore" and "I just don't give damn" were given by patients[62]. "I have told many psychiatrists and others interested in psychotherapy, '*Rauwolfia* is a good psychotherapy in pill form'"[35,36] from Langley Porter Clinic, San Francisco. Margolis[62] in a review on pharmacotherapy in psychiatry compared the efficacy of reserpine and chlorpromazine and concluded "It is generally agreed that for the most part chlorpromazine and reserpine influence essentially the same type of psychiatric illness".

Plummer *et al*[63] observed that reserpine exerted a calming and sedative action in a wide varieties of animals. They attributed this to an alternative in sympathetic – parasympathetic balance by partial suppression of the sympathetic predominance at the hypothalamus. Weiskrantz and Wilson[64] and Domino[65] attributed this to reserpine's action on the amygdala and the limbic system. Faucett *et al*[66] from Mayo Clinic summarized some of the pharmacological studies on *Rauwolfia* compounds. Healy and Savage[55] have reported that reserpine, which depletes monoamines may have autodepressant properties. They pointed out that it was used in a number of centres through the 1970s and 1980s in the management of refractory depression. Baumeister *et al*[67] while discussing the myth of reserpine-induced depression pointed out, "The discovery that reserpine depletes brain monoamines was an important factor in the development of monoamine hypothesis of depression and it continues to be widely cited in support of the hypothesis". They go on to add "This hypothesis ushered the modern biochemical paradigm into psychiatry and is still of great importance. It serves as a heuristic to guide research, it enhances psychiatry's prestige, and it helps to validate and promote drug therapy, for depression and other mental disorders"[67].

It is obvious from the above account that between 1930 and 1955 based on the initial work of Indian scientists, later adopted by those in the West, especially the USA, it was generally accepted that certain alkaloids of *R. serpentina,* especially reserpine/serpasil had hypotensive and sedative and tranquelizing properties without any significant adverse effects. However, most of the studies quoted above did not provide the pathophysiological basis of this effect during the same period and a large number of investigations were carried out to explore the mechanistic aspects of these therapeutically useful effects. These are discussed in the Part II of this paper.

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