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Assessment of *Nigella Sativa* Induced Adverse Drug Reactions

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ABSTRACT

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Objective: Monitoring of Adverse Drug Reactions (ADRs) with intake of *Nigella sativa* was carried out in a primary care Ayurvedic hospital. Patients were counseled and information regarding their medical and medication history was taken. **Methodology:** The people who were using *Nigella sativa* as drug were followed for a period of 6 months prospectively. Naranjo's algorithm, WHO probability scale, Modified Hartwig and Seigel scale and Modified Shumock and Thornton scales were employed to assess the Causality, Severity and Preventability of the ADRs.**Results:** At the end of the study 22 ADRs were observed with the usage of *Nigella sativa* for the maintenance of normal health. Among the ADRs 45.45% were found Possible and 54.54% were found Probable (Naranjo's algorithm). **Conclusion:** In assessment of severity level all the ADRs (100%) were mild and definitely preventable. Even with these ADRs, the medication was not discontinued but dose adjustment was done in all the cases.

Keywords: Seeds, Nigella *sativa,* Adverse Drug Reactions, Alternate Medicine.

INTRODUCTION

Drug is well defined as "Substance intended to be used for the diagnosis, treatment, mitigations or prevention of any disease or disorder in human beings or animals including topical preparations"[1] further holds the reputation for being extremely good as well as adversely bad. The Thalidomide tragedy in the early 60s of last century resulted in the withdrawal of the drug from the market by 1965 almost two decades after its introduction in year 1957 for morning sickness (pregnant women) is a good example of the adversity of a drug which resulted in congenital malformations in the new born.[2]

In the recent years, with the combined effort of researchers and healthcare professionals many more drugs with adverse drug reactions have been identified like aplastic anaemia by chloramphenicol, rhabdomyolysis by statins, depression by reserpine, thromboembolism by oral contraceptives etc.[2] hence, serious and unexpected adverse drug reactions associated with other drugs must be identified and brought to the book through a process known as pharmacovigilance.

Pharmacovigilance is defined as "The science and activities relating to the detection, assessment, understanding and prevention of adverse events or any other medicine related problems".[3]

Day by day, the drug usage is increasing steadily which is reflected in the economics merely ranging in billions of rupees. Out of which the total herbal market is of 3224 billion rupees approximately (62 billion dollars). India's contribution in the herbal global market is 1.61% i.e. 52 billion rupees (1 billion dollar).[4] There is an alarming sense of vigilance towards the usage of herbal medicine in India and the whole world, as the expected herbal medicine usage may rise to 5 trillion dollars by 2050.[4]

An adverse event shall be any unintended and unfavorable outcome associated with the use of a medicinal product.[5] Whereas, all noxious unintended responses to a medicinal product related to any dose is adverse drug reaction which is of two different types i.e. listed and unlisted adverse drug reaction.[5]

A very strong belief of alternate medicine being free of adverse drug reaction is misreading the fact that the alternate medicine also bears molecules which can potentially alter the physiology of humans.[6] However, it is an eye opening fact that identification of ADRs is age old practice explained very well in "*Charaka Samhitha*"[6,7] even explaining the demographic changes effects the action of drug on humans and plants selected.[6,7] so, the above said topic was planned.

The proposed study was aimed to achieve the following objectives 1) To ensure patient care and safety in relation to use of *Nigella Sativa* (black seed, black cumin) most commonly used herbal drug in the middle east countries for the treatment of ailments like asthma, allergic rhinitis, diarrhea, dyslipidaemia also used as hepatoptotective, Nephroprotective, Immunomodular etc,[20] but very less data is available in the south Indian population that is why the herb was selected for the study.

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METHODOLOGY

It is a non-randomized, prospective, observational study carried out at a primary care hospital at Kurnool district of Andhra Pradesh under the supervision of ayurvedic physicians. The present study was approved by Institutional human ethical committee of Raghavendra institute of Pharmaceutical education and research (RIPER/IRB/005/2012). The data collection and analysis of data was done for a period of 6 months After explaining the purpose, protocol, risk and benefit of the present study the inform consent were taken from the study subjects. Subjects those who are aged between 18 – 60 years with or without concomitant diseases were included in the study and bears inclusion criteria. Drugs were measured and prescribed by the Ayurvedic physician and dispensed and counseled by the qualified pharmacist.

Nigella Sativa Seed:

The indigenous variety of seeds of *Nigella sativa* were purchased commercially from local market and seeds were authenticated by the pharmacognosist of RIPER, Anantapur, Andhra Pradesh. The seeds were washed, dried, powdered and 500 mg of powdered drug was selected as dose for the common ailments like Infections, Fever, Arthritis etc.[21]

A total of 250 were registered, among which 60 were excluded from the study as they were not fulfilling the inclusion criteria. Remaining 190 patients were included in the study.

Well designed proforma was used as a data collection form which includes the details of demography, diagnostic and all details about medication (Dose, Frequency, Dosage form etc). The patients were monitored and complaints of ADRs were noted through direct interview once every week.

The causality of reaction was assessed by using Naranjo's algorithm [8] and WHO probability scale.[9] The severity and preventability of adverse drug reaction was assessed by modified Hartwig and Seigel scale[10] and Shumock and Thornton scale.[11]

RESULTS

A total of 190 patients with different clinical diagnosis (Table 1) were selected. Subjects with arthritis, pyrexia, algesia were prescribed with NSAIDS, subjects with infectious agents were prescribed with antibiotics 22 subjects expressed GI disturbances and rest had no complaints. Patients with gastric ulcers expressed adverse drug reactions with incidence rate of 11.5%, out of which 51.5% were male and 45.4% were female and 61% of all the patients were below 60 years of age and 38.9% were above 60 years of age. (Table 1)

The organ system affected predominantly by the adverse drug reaction is gastrointestinal track (11.5%) with majority being mild and was found definitely preventable. The suspected adverse drug reaction was also classified using WHO terms i.e. gastritis, heartburn (gastrointestinal effects by drug).

Causality association between drug and reaction was found possible with 54.54% (n=12) and probable with 45.45% (n=10) on Naranjo's scale respectively and 36.36% (n=8) and 63.63% (n=14) were found possible and probable on WHO adverse drug reaction probability scale respectively. Among the adverse drug reaction heartburn accounts for 81.81% (n=18) and heartburn with pointed pain in the gastric region accounts for 100% (n=22) of cases. The severity assessment showed that 22 (100%) adverse drug reaction were found to be mild – level 2 type. Preventability assessment showed that 22 (100%) adverse drug reaction were definitely preventable. (Table 2)

DISCUSSION

The compliant of GI inflammation may be attributed to different possible reasons primarily NSAIDS induced GI hemorrhage and the incidence rate of a meta analyzed different studies was found to be 0.12% [12] and the patients who were on both NSAIDS and *Nigella Sativa* may express GI discomfort because of additive effect of one agent over other.

Secondarily, the patients might be suffering from peptic ulcers which were not diagnosed. In such cases, the GI mucosal eradicated regions may be the primary spots of inflammation.

The number of adverse drug reaction involved with *Nigella Sativa* was 22 (Gastritis 8, heart burn 14) The Causality, Severity and Preventability of ADRs was studies by employing pre-standardized scales revealed that 45.45% cases were possible and 54.54% cases were probable ADRs with Naranjo's algorithm[8] whereas, 36.36% cases were possible and 63.63% cases were probable ADRs with WHO probability scale.[9] The severity of all the ADRs was of 'Mild-Level 2 type' (modified Hartwig and Seigel scale)[10] and found to be definitely preventable with preventability scale (Shumock and Thornton scale).[11] (Table – 02) Different research studies have concluded that drugs used in alternate system of medicine produces adverse drug reaction.[14] One common understandable point is that even plant extracts and preparations may consist of many different molecules which results in many different effects. But, the intensity of adverse drug reaction produced by alternate medicine shall be low because of concentration of molecules in the preparation.

Mildness of the reaction cannot be ignored because the identified reaction may be mild but the reaction which was not identified may project serious consequences even being mild.

Drugs like digoxin which is used as good choice in conditions like Congestive Cardiac Failure is given at a mild dose (mild concentration) is known to produce all types of Cardiac arrhythmias like atrial tachycardia, atrial fibrillation, ventricular tachycardia etc.[15] Seed of plant *Thevetia neriifolia* at very small amount can take life of an adult.[16] Tetradotoxins which is obtained from many groups of fishes and symbiotic bacteria like *"Pseudoalteromonas tetraodonis"* is a potent sodium channel blocker which further blocks the firing by the neurons at very small doses.[17]

Adverse drug reactions produced by any drug or formulation (Alternate medicine) alter the quality of life and increases pharmacoeconomic burden on the patients undergoing treatment.[18]

Certain drug-drug interaction between *Hypericum perforatum* a traditional medicine and allopathic medicine has resulted in identification of adverse drug reaction as the two drugs are metabolized by common enzyme system in liver. The market withdrawal of *Kava Kava* and *Aristolochia* because of liver and nephrotoxicity and carcinogenic potential is a classic example of alternate medicine possessing mild to severe adverse reactions.[19]

When patients were counseled it revealed that the subjects included in the study has followed a common procedure of taking the drug in empty stomach followed by the consumption of beverages like tea and milk. The said adverse drug reaction of *Nigella Sativa* may be a probable outcome of

Table 1: Details of Age, Sex, Co-morbidities of subjects and Adverse drug reactions of *Nigella Sativa*.

Age	**Number**	**Percentage**
Less than 60 years	116	61%
More than 60 years	74	38.9%
Sex	**Number**	**Percentage**
Males	98	51.5%
Females	92	48.4%
Co morbidities (%)	**Without co morbidities (%)**	
Males – 10 (5.2%)	Males – 88 (46.3%)	
Females – 12 (6.3%)	Females – 80 (42.1%)	
Clinical Diagnosis	Arthritis - 44 (23.15%)	
	Fever – 58 (30.52%)	
	Infections – 28 (14.73)	
	Asthma – 11 (5.7%)	
	Renal Calculi – 30 (15.78%)	
	Constipation – 05 (2.63%)	
	Sinusitis – 05 (2.63%)	
	Aesthetics problems – 09 (4.73%)	
Total number of patients	**Adverse Drug Reactions**	**Percentage ADRs**
190	22	11.5%

Table 2: Causality, Severity and Preventability of Adverse Drug Reactions.

Sl No	**Naranjo's Causality Assessment**
1	Possible 45.45% (n=10)
	Probable 54.54% (n=12)
2	**Who Causality Assessment**
	Possible 36.36% (n=8)
	Probable 63.63 % (n=14)
3	**Severity Assessment (modified Hartwig and Seigel acale)**
	Mild – Level 2 type
4	**Preventability Assessment (Shumock and Thornton scale)**
	Definitely Preventable

Drug-Drug and Drug-Food interaction for which patients were not treated but counseling was given on drug administration as the adverse drug reaction was mild and self limiting. In some cases patients accepted the fact that drug may produce complications in empty stomach but not ready to withdraw the drug because of its beneficial effects.

The study was planned and carried for duration of six months and we were able to identify few reactions. Long duration study helps in finding the incidence, prevalence and predisposing factors resulting in adverse drug reaction.

CONCLUSION

In this present study, the usage of *Nigella Sativa* for better health outcome was studied. The drug has shown adverse drug reaction related to gastrointestinal tract, with change in time of intake of drug may prevent adverse drug reaction.

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