ABSTRACT
Erectile dysfunction is the inability to achieve or maintain penile erection, sufficient for satisfactory sexual performance and the prevalence of ED is age dependent and increases with advancing age. The presence of a normal sexual desire and the inability to physically act on that desire affect patients’ lives severely, which makes ED a major QOL issue. This study was conducted to evaluate the efficacy and safety of “Tentex Royal” in patients with ED.

This study was a prospective, open, non-comparative, phase III clinical trial, and was conducted as per the ethical guidelines of Declaration of Helsinki. A total of 30 patients, who were suffering from ED and who were willing to give informed written consent were included in the study. Patients with ED were included in the study and the patients were selected by giving a list of questionnaire eliciting the sexual activity, viz., “Ability to achieve erections”, “Ability to maintain erections”, “Frequency of orgasm” and “Satisfaction with sexual relationship”.

Patients with a history of myocardial infarction, genital anatomical abnormalities, concurrent conditions that would prohibit sexual intercourse and those patients who were not willing to give informed consent were excluded from the study. Similarly, patients consuming specific medications and patients with severe cardiovascular, renal or hepatic impairment were also excluded from the study. All the patients underwent thorough clinical and biochemical examinations. All the patients were advised to consume 2 capsules of “Tentex Royal”, once daily, one hour before the sexual intercourse. All the patients were followed up every week and the evaluation of EF domain scores was recorded at the end of every week and the completion of 6 weeks of treatment. The predefined primary efficacy endpoint was increase in the EF scores at the end of 6 weeks and the predefined secondary safety (short- and long-term) endpoints were reduced incidence of adverse events and overall patient compliance to the drug therapy. All the adverse events either reported or observed by the patients were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Relation of adverse events to the study medication was predefined as “Unrelated”, “Possible” and “Probable”. Statistical analysis was done according to intent-to-treat principles. The minimum level of significance was fixed at 99% confidence limit and a two-sided "p" value of <0.001 was considered as significant.

There was a significant improvement in the mean score for “Ability to achieve erections” from the 3rd week onwards, and a highly significant improvement in “Ability to maintain
erections”, “Frequency of orgasm” and “Satisfaction with sexual relationship” from the 4th week onwards, as compared to the baseline mean score and the trend continued till end of the study. Furthermore, there were no clinically significant changes in the hematological and biochemical parameters, and there were no clinically significant adverse reactions, which is reflected in the excellent patient compliance. These effects might be due to the synergistic actions of the ingredients of “Tentex Royal”. Therefore, it can be concluded that “Tentex Royal” is clinically effective and safe in the management of ED.

INTRODUCTION
Erectile dysfunction is the inability to achieve or maintain penile erection, sufficient for satisfactory sexual performance, and approximately 150 million men worldwide suffer from some degree of ED. In one study, done amongst men aged 40 to 70 years, the prevalence of “mild ED” was found to be 52%, of “moderate ED” was found to be 25%, and of “severe ED” was found to be 10%. The prevalence of ED is age dependent and increases with advancing age (among men aged 40 years, it is 5%, while among those aged 70 years the same is 15%). Erectile dysfunction is a multifactorial disease and is influenced by increasing age, hypertension, diabetes, cardiovascular health, obesity, dyslipidemia and life style factors (cigarette smoking and alcohol use). Erectile dysfunction occurs at an earlier age in men with diabetes than in men in the general population, and several studies have demonstrated a high prevalence (35% to 75%) of ED in diabetics. It has been estimated that >50% of diabetic men develop ED within 10 years of being diagnosed with diabetes and the incidence of ED increases from 9% in diabetic men in the age group 20-29 years to 95% in men >70 years of age. Similarly, it also been documented that a 3rd of men experience ED after nerve sparing radical retropubic prostatectomy (NS-RRP). The presence of a normal sexual desire and the inability to physically act on that desire affects patients’ lives severely and various disorders like stress in interpersonal relationships, problems with partners and increase in mental stress make ED a major QOL issue.

“Tentex Royal” is a polyherbal formulation, which is recommended for the management of the ED, and “Tentex Royal” contains the extracts of Tribulus terrestris and powders of Asteracantha longifolia, Prunus amygdalus, Blepharis edulis, Curculigo orchioides, Crocus sativus, processed in Curculigo orchioides and Piper betle. This study was conducted to evaluate the efficacy and safety of “Tentex Royal” in patients with ED.

Study aim
This study trial was planned to evaluate the efficacy and safety (short- and long-term) of “Tentex Royal” in patients with ED.

MATERIALS AND METHODS
Study design
This study was a prospective, open, non-comparative, phase III clinical trial and was conducted at the Heritage Hospital, Varanasi, India, as per the ethical guidelines of Declaration of Helsinki. The study protocol, case record forms, regulatory clearance documents, product related information and informed consent forms were submitted to the ‘Institutional Ethics Committee’, and were approved by the same.

Inclusion criteria
A total of 30 patients, who were suffering from ED, and who were willing to give informed written consent were included in the study. For inclusion in the study, rate of successful intercourse was analyzed according to the specially designed questionnaire. The list of
questions included were “Ability to achieve erections”, “Ability to maintain erections”,
“Frequency of orgasm” and “Satisfaction with sexual relationship”.

Exclusion criteria
Patients with a history of myocardial infarction, genital anatomical abnormalities, concurrent
conditions that would prohibit sexual intercourse and those patients who were not willing to
give informed consent were excluded from the study. Similarly, patients consuming specific
medications like androgen suppression therapy (leuprolide or goserelin), antiandrogen therapy
(bicalutamide, flutamide or nilutamide), or estrogenic therapy (diethylstilbestrol), nitrates,
ketocanazole, itraconazole, erythromycin, and patients with severe cardiovascular, renal or
hepatic impairment were also excluded from the study. Also, patients consuming sildenafil or
using any intracorporeal, intraurethral, topical or oral agents for ED were excluded from the
study.

Study procedure
At the enrolment visit, a detailed medical history, with special emphasis on sexual life, was
obtained from all the patients. At the end of each week of treatment, a set of questions were
asked to elicit the patients’ responses for the following parameters:

1. Ability to achieve erections
2. Ability to maintain erections
3. Frequency of orgasm
4. Satisfaction with sexual relationship

Based on the responses to these questions, the following scoring was given: Extremely
satisfied: 3, Very satisfied: 2, Satisfied: 1, Not satisfied: 0.

All the patients underwent a thorough clinical and biochemical examination (hemogram,
blood sugar, lipid profile, liver function tests and renal function tests). All the patients were
advised to consume 2 capsules of “Tentex Royal”, once daily, one hour before the sexual
intercourse.

Follow-up and assessment
All the patients were followed up every week, and the ‘EF domain score’ was recorded at the
end of every week and after the completion of 6 weeks of treatment.

Primary and secondary endpoints
The predefined primary efficacy endpoint was increase in the EF domain score at the end of
the study period. The predefined secondary safety (short- and long-term) endpoints were
reduced incidence of adverse events and overall patient compliance to the drug therapy.

Adverse events
All the adverse events either reported or observed by the patients were recorded with
information about severity, date of onset, duration and action taken regarding the study drug.
Relation of adverse events to study medication was predefined as “Unrelated” (a reaction that
does not follow a reasonable temporal sequence from the time of administration of the drug),
“Possible” (follows a known response pattern to the suspected drug, but could have been
produced by the patient’s clinical state or other modes of therapy administered to the patient),
and “Probable” (follows a known response pattern to the suspected drug that could not be
reasonably explained by the known characteristics of the patient’s clinical state).
Patients were allowed to withdraw voluntarily from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, and the reasons for non-compliance were noted.

**Statistical analysis**
Statistical analysis was done according to intent-to-treat principles. "Repeated Measures ANOVA Test" and "Bonferroni’s Multiple Comparison Test" evaluated the changes in the baseline values and the values after 1st, 2nd, 3rd, 4th, 5th and 6th week. The minimum level of significance was fixed at 99% confidence limit and a two-sided "p" value of <0.001 was considered as significant.

**RESULTS**
A total of 30 patients between the age group of 40 to 60 years were included in the study (Table 1). There was a significant improvement in the mean score for “Ability to achieve erections” from the 3rd week onwards, as compared to the baseline mean score and the trend continued till end of the study (“Repeated measures ANOVA Test” statistics: F=20.29, R²=0.4117, p<0.05; S; & “Post test for linear trend” statistics: Slope=0.2155, R²=0.2128, p<0.0001; HS) (Table 2).

Similarly, there was a highly significant improvement in the mean score for “Ability to maintain erections” from the 4th week onwards, as compared to the baseline mean score and the trend continued till end of the study (“Repeated measures ANOVA Test” statistics: F=13.53, R²=0.3181, p<0.0001; HS; & “Post test for linear trend” statistics: Slope=0.1595, R²=0.1265, p<0.0001; HS) (Table 2).

| Table 1: Baseline characteristics of enrolled patients |
|-----------------|-----------------|
| Age range (years) | 40-60 |
| No. of patients | 30 |
| Aetiology | Organic | 20 |
| | Psychogenic | 6 |
| | Mixed | 4 |
| Medical history | History of Smoking | 25 |
| | Hypertension | 22 |
| | Diabetes | 12 |
| | Depressive disorder | 3 |
| Concomitant medication | Beta blocker | 12 |
| | Renin-angiotensin system acting agent | 3 |
| | Calcium-channel blockers | 8 |
| | Serum lipid –reducing agents | 6 |
| | Diuretics | 4 |
| | Other anti-hypertensive agents | 4 |

| Table 2: Improvement in the parameters of sexual activity on treatment with Tentex Royal |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Parameters | Ability to achieve erections | Ability to maintain erections | Frequency of orgasm | Satisfaction with sexual relationship |
| Repeated measures ANOVA | F=20.29 | 13.53 | 6.329 | 9.893 |
| | R²=0.4117 | p<0.05 | p<0.0001 | p<0.0001 |
| Significance | Significant | Highly significant | Highly significant | Highly significant |
| Post test for linear trend | Slope=0.2155 | 0.1595 | 0.9405 | 0.07381 |
| | R²=0.2128 | 0.1265 | 0.04393 | 0.08729 |
| | p value | p<0.0001 | p<0.0001 | p<0.0001 |
| Significance | Highly significant | Highly significant | Highly significant | Highly significant |
There was a highly significant improvement in the mean score for “Frequency of orgasm” from the 4th week onwards, as compared to the baseline mean score and the trend continued till end of the study (“Repeated measures ANOVA Test” statistics: $F=6.329$, $R^2=0.1791$, $p<0.0001$; HS; & “Post test for linear trend” statistics: Slope=0.9405, $R^2=0.04393$, $p<0.0001$; HS) (Table 2).

Also, there was a highly significant improvement in the mean score for “Satisfaction with sexual relationship” from the 4th week onwards, as compared to the baseline mean score and the trend continued till end of the study (“Repeated measures ANOVA Test” statistics: $F=9.893$, $R^2=0.2544$, $p<0.0001$; HS; & “Post test for linear trend” statistics: Slope=0.07381, $R^2=0.08729$, $p<0.0001$; HS) (Table 2).

There were no clinically significant changes in the hematological and biochemical parameters. There were no clinically significant adverse reactions; either reported by the patients, or observed by the investigators and the overall compliance to the treatment was excellent.

**DISCUSSION**

Penile erection is a hemodynamic event, which is dependent on the relaxation of smooth muscles and arteries of the corpus cavernosum. Relaxation of corpus cavernosal smooth muscle is mediated by NO–induced cGMP formation. In response to sexual stimuli, the noradrenergic nerves, noncholinergic nerves and endothelial cells of the penile arterioles release NO, which induces smooth muscle relaxation via stimulation of guanylate cyclase and the production of cGMP.

The risk for ED increases progressively with advancing age. The causes of ED are divided into 3 broad categories, viz. “Psychogenic ED”, “Organic ED” and “Mixed ED”. Psychogenic factors are involved alone or in combination with organic causes in substantial number of cases. Organic ED results from neurologic, hormonal and vascular pathologies. Erectile dysfunction is also commonly associated with a number of other diseases frequently occurring in aging men like benign prostatic hyperplasia, hypertension, ischemic heart disease, peripheral vascular disease, atherosclerosis, dyslipidemia, and diabetes mellitus. In men with diminished libido, an endocrine mechanism (hypogonadism, hyperprolactinemia or DHEA deficiency) may be at work. Neurologic origins of ED include peripheral autonomic (cavernous nerve) or somatic (dorsal and pudendal nerve) neuropathy associated with diabetes, alcoholism, vitamin deficiencies, infectious diseases and spinal cord injury.

Manifestation of ED can also be due to a variety of drugs such as antihypertensives (beta-blockers and thiazides), antimicrobials (ketoconazole and derivatives), allopurinol, antiepileptics, antipsychotics, opiates, anxiolytics, glycosides, cholesterol synthesis inhibitors, fibric acid derivatives, antiulcerants (cimetidine and omeprazole) and drugs interfering with the activities of androgens (finasteride or cyproterone), all of which may interfere with EF.

The incidence of ED increases with diabetes, hypertension, hypercholesterolemia, cardiovascular disease and renal failure, and all these conditions are associated with endothelial dysfunction. Increased inactivation of NO by superoxide results in impaired penile NO transmission and smooth muscle relaxation. Furthermore, propagation of endothelial dysfunction by reactive oxygen species may result in chronic impairment of penile vascular function, a process analogous to early atherogenesis. In one study, erectile function
was assessed by measuring the rise in intracavernous pressure following supplementation with antioxidants and the penile tissue was evaluated for neuronal NO synthase, smooth muscle alpha-actin, nitrotyrosine and endothelial cell integrity. The study showed that adequate concentrations of the oxygen free radical scavenger vitamin E, enhanced levels of circulating NO and improved the erectile function. Therefore, these studies suggest that antioxidants have a role to play in alleviating ED.

This study observed significant improvement in the mean score for “Ability to achieve erections”, “Ability to maintain erections”, “Frequency of orgasm” and “Satisfaction with sexual relationship”. Also, there were no clinically significant changes in the hematological and biochemical parameters and there were no clinically significant adverse reactions; which is reflected in the excellent patient compliance to the treatment. These beneficial effects of “Tentex Royal” might have been due to the ingredients, which are well researched and documented by various researchers.

The principle ingredients of Tribulus terrestris are saponins (terrestrins A and B) and galactopyranosides. The active ingredients of Prunus amygdalus are polyphenols, flavonoids, anthocyanins, chlorogenic acid and quercetins. The principle ingredient of Crocus sativus is a carotenoid (crocetin) and is characterized by a diterpenic and symmetrical structure with seven double bonds and four methyl groups. The active ingredients of Curculigo orchioides are triterpene glycosides (curculigosaponins G, H, J, and I).

Dihydroepiandrosterone has been demonstrated to have an antiatherosclerotic effect in animal models. Protodioscin, a phytochemical derived from Tribulus terrestris is converted to DHEA, and it has been observed that DHEA improves flow-mediated dilation of the artery (a function dependent on endothelium-derived nitric oxide). Tribulus terrestris enhances the relaxant effect on corpus cavernosum due to an increase in the release of NO from the endothelium and nerve endings. Curculigo orchioides also has similar androgenic action.

Crocus sativus and Prunus amygdalus are potent antioxidant agents and reduce the lipid peroxidation with a concomitant increase in enzymatic activity of superoxide dismutase, catalase and glutathione peroxidase.

CONCLUSION
Erectile dysfunction is the inability to achieve or maintain penile erection, sufficient for satisfactory sexual performance and the prevalence of ED is age dependent and increases with advancing age. The presence of a normal sexual desire and the inability to physically act on that desire affects patients’ lives severely and various disorders like stress in interpersonal relationships, problems with partners and increase in mental stress make ED a major QOL issue. This study was conducted to evaluate the efficacy and safety of “Tentex Royal” in patients with ED.

This study observed highly significant improvement in the mean score for “Ability to achieve erections” from the 3rd week onwards, and a highly significant improvement in the mean scores for “Ability to maintain erections”, “Frequency of orgasm” and “Satisfaction with sexual relationship” from the 4th week onwards, as compared to the baseline mean score. Furthermore, there were no clinically significant changes in the hematological and biochemical parameters and there were no clinically significant adverse reactions, which is reflected in the excellent patient compliance. These effects might be due to the synergistic
actions of the ingredients of “Tentex Royal”. Therefore, it can be concluded that “Tentex Royal” is clinically effective and safe in the management of ED.

REFERENCES