CHAPTER 1

INTRODUCTION

Contraceptive practice has undergone a revolution in the past 25 years following the development of oral hormonal contraceptives, IUDs and technological advances in male and female sterilization (Zatuchni et al., 1980; Zatuchni, 1983). Accompanying this contraceptive revolution is a significant increase in the social awareness of unwanted pregnancies. Moreover, these methods of family planning have cleared many religious, social and cultural barriers. In the past, emphasis had been laid on the development and use of contraceptive methods for female only. Recent concern over the side effects from oral contraceptive agents and an increasing willingness of the male to share the responsibility of family planning have increased interest in the development of some effective, safe, advantageous and acceptable method of male contraception which is reversible.

Different methods of fertility regulation that are currently under investigation and development include (i) pharmacological methods that interfere with sperm production and maturation, (ii) methods that block sperm transport in
the male and female reproductive tracts, (iii) intrauterine devices and (iv) immunological approaches for fertility control.

In the first method, a large number of chemical compounds and pharmacologic agents both steroidal and non-steroidal, have been shown to cause direct or indirect interference with the process of spermatogenesis (Hafez 1976; Zatuchni et al., 1980; Mann and Mann, 1981). The first chemical compounds tested for their potential application as contraceptives were the nitrofuranes, commonly used to treat urinary tract infections (Albert et al., 1975). Unfortunately undesirable effects precluded their development (Zatuchni, 1983).

Following this α-chlorohydrin and other chlorinated sugars were tested. These exhibited rapidly reversible antifertility effects among many animals tested including sub-human primates (Gomes, 1970). The antifertility effects of α-chlorohydrin are usually seen within days of treatment and are associated with depressed sperm motility and decreased oxygen consumption by sperm (Vickery et al., 1974; Brown-Woodman and White, 1975; Mohri et al., 1975). Unfortunately these compounds and their metabolites were found in high concentration in cerebrospinal fluid. It was thought that these might cause
inhibition of glucose utilization mechanism. Thus their use in human beings was not recommended (Ericsson, 1970; Lobal et al., 1980; Mann and Mann, 1981; Zatuchni, 1983).

The use of antiandrogens to reduce mammalian fertility depends on the antagonism of androgen-supported testicular or epididymal function without simultaneously reducing libido (Gomes, 1970) Some investigators studied the effect of the antiandrogen cyproterone acetate in animals including men (Prasad et al., 1970; Roy et al., 1976; Foegh et al., 1979; Wang and Yeung, 1980; Moltz et al., 1980). Administration of cyproterone acetate led to infertility without apparent loss of libido or spermatogenesis. The drug affected epididymal sperm maturation with the result the sperm lost their fertilizing capacity and motility (Rajalakshmi et al., 1971). However, large doses of the chemical are required to induce such a condition, and these high levels affect other androgen target tissues as well. Morse et al. (1973), reported that high doses of cyproterone acetate reduces libido in men. Therefore, the use of this class of compounds was also found unsuitable.

The antigonadotropic effects of sex steroids have been studied for a number of years. Certain gonadal steroid hormones produce oligospermia or azoospermia (Lee et al., 1979; Bain et al., 1980; Foegh et al., 1980a). This action results due to decreased synthesis and/or release of
pituitary gonadotropins or due to local testicular effects. The sex steroids investigated include estrogens, progestins and androgens (Briggs and Briggs, 1974; Foegh et al., 1980b; Paulsen, 1986). The estrogens obviously are not acceptable for use in males because of their feminizing effects (Ericsson and Dutt, 1965; Patanelli, 1975; de Kretser, 1974, 1978). All these steroidal compounds although capable of regulating male fertility, are also known to affect non-reproductive tissues.

Keeping all this in view, it would be of great value to develop fertility inhibitors that are totally selective for the reproductive system. It is possible that a plant derived drug may prove this effect (Farnsworth and Waller, 1982). Significant steps have already been taken by World Health Organisation to carry out research aimed at finding new and effective fertility regulating agents from plants. The plant kingdom has abundant chemical compounds that elicit pronounced effects in animals and humans (Raffauf, 1970; Windholz, 1976).

One advantage in developing a male antifertility agent from a plant source, rather than through the complete synthesis of a new drug, is that the plants might have been used in an indigenous medicinal system and may have a long folkloric history with established low toxicity potential (Farnsworth and Waller, 1982). India has a rich heritage and literature on the uses of plants for medicinal purposes.
Ancient Indian literature abounds with information of plants reputed to have sterilizing and abortificient properties (Kirtikar and Basu, 1935; Chopra, et al., 1949, 1958; Nandkarni and Nandkarni, 1954). Therefore, it is not unreasonable to believe that the plant kingdom should yield an effective antifertility drug (de Laszlo and Henshaw, 1954; Chaudhury and Vohra, 1970; Farnsworth et al., 1975a). Farnsworth and Bingel (1977) and Farnsworth and Waller (1982) have reviewed the potential value of plants as sources of new antifertility agents.

In 1970s, Chinese workers discovered that gossypol, a polyphenolic pigment isolated from cotton seeds, exerts remarkable antifertility effect on males of a number of animal species including man (National Co-ordinating Group, 1978; Chang et al., 1980; Kulkarni, 1982). This has led to its being investigated as a potential male contraceptive agent. But in early 1980, a number of side effects were reported in volunteers of gossypol (National Co-ordinating Group, 1978; Matlin et al., 1985). Alarmed by these serious side effects a number of other workers tried some other plant products as sources of new antifertility agents.

A number of plant extracts such as Cannabis extract (Miras, 1965 and Dixit et al., 1976); Hippophae salicifolia extract (Joshi et al., 1976); Aristolochia indica extract (Pakrashi and Pakrashi, 1977); Memordica
charantia extract (Dixit et al., 1978); Calotropis procera extract (Garg, 1979); Abrus precatorius extract (Baijal and Mathur, 1981); Ocimum sanctum extract (Seth et al., 1981); Malva viscus conszattii flower extract (Dixit, 1977; Verma et al., 1980; Joshi et al., 1981); Vinca rosea extract (Chauhan et al., 1979); plumbagin (Bhargava, 1984); solasodine (Dixit and Gupta, 1982a and Gupta et al., 1986); Spindus trifoliatus extract (Dixit and Gupta, 1982b and Bhargava, 1986) and Celastrus paniculatus extract (Wangoo and Bidwai, 1988) have been tried for fertility regulation. Many plants of the family Leguminasae and Rannunculacae have also been reported to possess antifertility activity (Farnsworth et al., 1975a; Baijal and Mathur, 1981; Baijal et al., 1981). Apart from these there are enormous number of plants which have been screened for their antifertility effects (Prakash and Mathur, 1976; Setty et al., 1976; Garg et al., 1978; Farnsworth and Waller, 1982; Kamboj and Dhawan, 1982 and Bhargava, 1988).

The plant derived compound, embelin, (2,5-dihydroxy-3-undecyl-1, 4-benzoquinone Fig.1) has recently been reported to induce sterility in mice (Munshi and Rao, 1972 and Munshi et al., 1972) and dog (Dixit and Bhargava, 1983). According to Ayurveda the fruit is dry with a sharp bitter taste; good appetiser, carminative, anthelmintic, alexiteric, laxative, alterative; cures tumours, ascites, bronchitis, mental diseases, dyspnaea, diseases of the
(2,5-dihydroxy-3-undecyl-p-benzo-quinone)
Embelin
FIG. 1
heart, urinary discharges, used in snake bites, jaundice, hemicrania, worms in wounds (Kirtikar and Basu, 1984). Moreover Bhargava (1988) has recommended that embelin can be used by human males without risk because of its non-toxicity.

Encouraged by these observations the present investigation was designed to establish the male antifertility potential of embelin isolated from the berry fruits of plant Embelia ribes Burm of family Myrsinaceae.

For this work, histological, cytochemical and biochemical studies of the testis and the accessory organs have been made to find out the mechanism and site of drug action. Metabolism of testes and accessory reproductive organs has been studied in detail. This is achieved through the study of sequential biochemical changes in the levels of lipids, proteins, glycogen and enzymes associated with their metabolism. In addition, a detailed study on the sperm morphology and percent motility have been made. For studying the side effects of the drug, changes in the levels of serum transaminases, phosphatases, bilirubin, cholesterol, albumin/globulin ratio, total lipids, free fatty acids (FFA), triglycerides (TG), cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C) have also been observed. This has been used as an
index to study the liver functions during treatment and recovery periods. In addition to all this, the effect of embelin on intestinal absorption has also been undertaken.