Novel spermicidal agent- A review

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ABSTRACT

Spermicides are chemical agents that immobilize/kill the spermatozoa in the vagina and exert their contraceptive effect in the female genital tract. Since most of the work on successful contraception concerns with ova. However, recent clinical trials have shown that detergent spermicides do not provide any protection against STDs and AIDS but may in fact even promote their transmission. The most commonly used compound is the neutral surfactant nonoxynol-9. Other spermicidal products which are structurally related to compound octoxynol or an alternative type of non-ionic surfactant, p-di-isobutyl-phenoxypolyethoxyethanol. Till no other natural or synthetic moieties are not available against sperms. Further recent advances are going on spermicidal activity in plants however success is not found. As it is suggested that sperm membrane sulfhydryl groups are important entities of the membrane and can be used as a tool for infertility assessment in unexplained male infertility and can be targeted for contraceptive research.

Key Words: Spermicidal, HIV, STD, Contraceptive, Surfactants.

INTRODUCTION

Today’s major problem, world facing is the rapid growth of population. The present population of world crossed 6.9 billion as per the statistics present [1]. India is not an exceptional in comparison to other countries. The present population status of India has crossed 100 crores and is still increasing day by day. In order to get control on this rapid growth the major programs introduced by Government of India include family planning programmes.
One of the primary concerns of family planning is spacing children and preventing unwanted pregnancies. Under the present global situation, in most parts of the world the need for deferring childbirth has been felt basically for the following reasons.

- Large families.
- Have proper spacing between childbirths which would permit their proper care.
- On health grounds for both mother and child.

Nowadays, various methods have been used and are evolved to prevent unwanted pregnancies. These methods of contraception are physical and chemical approaches used by males and females. Although such agents are in use as vaginal contraceptives but their development is still far from perfection. Till now none of the approaches can be considered as ideal. Hormone based methods may be considered as foolproof but suffer the drawback of causing undesirable side effects. Gynecologists prefer to prescribe oral contraceptives pills as the safest drugs for preventing unwanted pregnancies. However this is the time to give a look at spermicides having dual action, they act as contraceptives as well as alarming in sex related infectious diseases. The most of sexually transmitted diseases (STD) like acquired immunodeficiency syndrome (AIDS) infected peoples are required the development of spermicides having action of destroying infections of STD and AIDS [2].

**Spermicides**

Spermicides are chemical agents that immobilize/kill the spermatozoa in the vagina and exert contraceptive effect in the female genital tract. To effectively blockage of sperm migration, the spermicidal agent would have to act rapidly to prevent the penetration of spermatozoa into the endo cervical canal of uterus as well as to attack sperm present in the vaginal flora. Spermicide acting on a wide range of organism likes *N. gonorrhea, T. pallidum* and other species [3]. The failure of a vaginal contraceptive is often due to mistakes in the application of spermicide rather than its poor contraceptive efficacy. Once sperm are released vaginally, they may pass within minutes into the cervix at mid-cycle and starts their transport through the female genital tract. Therefore, the available time for vaginal contraceptive exert their spermicidal activity *in-vivo* is relatively short. Vaginal contraceptives must be nonirritating to the vaginal and penile mucosa, should not have any adverse effect on the developing embryo or fetus and must be free of toxicity, however it should also be systemically nontoxic [4].

**Detergents as spermicides**

Detergents lead to spermicidal preparations that are available over the counter. Out of which a few of these detergents have also shown substantial microbicidal properties [5-7]. However, a number of studies have now shown that detergent spermicides do not provide any protection against STDs including AIDS [8], but may in fact even promote their transmission [9–11]. This is largely due to the surfactant nature of the chemical that irritates the epithelium membrane of vagina and causes lesions due to repeated use, making the vagina more susceptible to STD infections [12–13]. It has also been shown that nonoxynol-9 (the most commonly used detergent spermicide) kills the natural vaginal flora (Lactobacillus) [14-18] causing disturbance of the normal (acidic) vaginal pH and weakening of the natural protection against STIs, reproductive-tract infections (RTIs) and urinary-tract infections (UTIs) [19-24].
Microbicidal spermicide:
Protection against unwanted pregnancy remains the primary concern of women during every sexual act and defense against STDs may be of secondary concern. If a microbicidal cream does not protect against pregnancy, it may not be used continuously. To achieve the desired family size, a fertile woman must practice birth control throughout most of her potential reproductive years—as many as 30-36 years between menarche and menopause [25].

Need of new generation spermicides:
A new generation of dual-function spermicides that offer protection against STIs (including HIV) and pregnancy [13, 26]. Current use of OCPs and IUDs is becoming restricted over the world due to increased side-effects. The use of vaginal contraceptives as local (topical) agents in a need-based manner (not requiring regular intake/application) makes safer. A microbicidal spermicide can also be used as an adjunct to condoms or in medicating condoms to increase their efficacy and safety [27]. Thus, an ideal spermicide should have preferably a nondetergent/ nonsurfactant molecule, which is nonirritant, aqueous soluble, a good cervical mucus biodiffusion with microbicidal (including anti-HIV) activity, and is non hostile to vaginal flora. In the upper genital tract, infection with Chlamydia trachomatis is the commonest cause worldwide of pelvic inflammatory disease (PID) in women and consequent infertility. However, the incidence has not been well defined [28-29].

When evaluating whether the use of particular method of contraception is associated with an increased or decreased risk of STD, it is important to be aware of the confounding factors and potential conflicts which may be present in epidemiological, cohort, or case/control studies. Those who choose, for instance, to use condoms may do so because they are more aware of their need for protection from STD. Professional advice is also given according to perceived risk factors. The Pills are used by most of sexually active women under 25 years old and is not restricted to those in a stable relationship. While, the intrauterine device (IUD) is generally recommended only for long-term, stable relationship and without other risk factors for PID.

Even a moderate quantity of spermicidal agent with excellent efficacy to prevent STD and AIDS could be used for medicating condoms. The classical criteria for designing a spermicidal agent relates to the ability of the test compounds to spontaneously kill the spermatozoa in pH independent mechanism without damaging the surrounding tissue. Evidence indicates that the entry of human immunodeficiency virus requires the sequential interaction of the viral exterior enveloped glycoprotein gp-120 with CD-4 glycoprotein and the chemokine receptor on the cell surface [6]. The current world population is expected to increase by more than 50% by the year 2050 [1]. Nonoxynol-9 (N-9), the most widely used spermicide in contraceptive preparations displayed excellent microbicidal activity in-vitro [28-30]. However recent clinical trials have shown that N-9 does not offer any protection against STDs and HIV, but on the same side it increases the risk of their transmission [26, 31-32]. Since surfactant like action of N-9 has been held responsible for this anomaly, efforts have been made to develop new dually active non-detergent agents that are devoid of the disadvantages of Nonoxynol [3-5, 33-39].

Spermicidal agents:
Acrylophenones, quinolines and dithiocarbamates are the structural classes that have been reported [6] as potent, non-detergent spermicides. Moreover, (E)-4-hydroxy-2-nonenal, a lipid
peroxide end-product, exhibits spermicidal activity without disrupting the sperm membrane by reacting with free sulfhydryl groups of sulfur bearing amino acids on sperm axonemal microtubules [7]. Similarly, specific sulfhydryl alkylating agents like N-alkylmaleimide derivatives, possess spermicidal activity [8-9]. Thus, sulfhydryl interactions play a vital role in spermicidal action.

Paroxetine (I) (arylmethylaryloxyypiperidine) and fluoxetine (II) (aryloxyphenylpropyamine) which are Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants can interact with neuronal 5-HT transporters via sulfhydryl binding [8]. They have been recently reported as non-detergent spermicides [10]. Besides, these several substituted aryloxyalkanols [11] (III), aminohydroxy alkyl derivatives [14] and substituted arylethylamines have also been shown to exhibit significant spermicidal activity.

The compounds (I, II, III) are benzenepropanamine analogues are spermicidal in nature. Since Trichomoniasis and Candidiasis are amongst the most common reproductive tract infections that cause morbidity, hence these compounds evaluate for their anti-candidal as well as antitrichomonas activity [15]. Structural changes have been made at position-1 and at 3-amino function. Dialkylamino moiety has been incorporated at position-3 because some piperazine derivatives have shown spermicidal activity [16-17].

During development of novel dual-functioning spermicides, S.T.V.S Kiran. et al. [30] reported that fluoxetine showed spermicidal as well as antitrichomonas activities. The modifications in fluoxetine structure I; (Fig. 1) may lead to compounds having spermicidal as well as anti-STI and other activities. Since the modifications at position-1 also leads to compounds with spermicidal, antifungal and anti-STI activities [32].
The Status of Spermicidal Agents:
Some synthetic and natural products have been studied for their spermicidal activity. According to their mode of action these can be broadly be classified into following categories:

1. Electrolytes: Electrolytes are agent which cause disruption of tonicity of spermatozoal cell wall and results in decreased spermicidal activity. The prominent examples are boric and tartaric acids, which generate foaming action to exert their spermicidal effect [26]. EDTA (1), a cationic chelating agent having spermicidal activity by modulating calcium ion concentration in semen [33].

![Chemical Structure of EDTA](image)

Myristamido propyl dimethyl benzyl ammonium chloride can be used as spermicides, anti-HIV agents or antiseptics [34]. Potash Alum solution have different effects on sperm at different concentrations. Ethonium-1,2-ethylene-bis-(N-dimethylcarbacyloxy methyl)-ammonium chloride (2) has showed very good spermicidal activity [35].

![Chemical Structure of Ethonium chloride](image)

2. Sulphydryl Binding Agents: The plasma membrane, head and tail region contain various proteins rich in disulfide linkages. The dynamic conversion of thiols to disulfide linkages forms an essential part of sperm maturation. Sulphydryl binding agents exert their action by oxidation,
alkylation or formation of mercaptides. Hydrogen peroxide, o-iodobenzoate and several hydroquinones are known to destroy the tertiary protein structure by converting the thiol group of cysteine to disulphide linkages. Phenyl mercuric acid is another mercaptide forming agent.

3.

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\text{Fluorescein-5-Maleimide}
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Maleimide derivatives (3) have been evaluated as spermicidal agents by inhibiting sperm motility [36].

4. Bactericides: This class consisted primarily of bactericides, which are often spermicidal because of their ability to interact with membrane components. eg. benzalkonium chloride [37-38] (4).

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\text{R= Mainly C}_{12}\text{H}_{25} \\
\text{C}_{14} \text{ and C}_{16} \text{ compounds are also used in preparation}
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Piperazine dicarboxamidine (5) derivatives are very good bactericides, fungicides and spermicides [25].

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\text{Quaternary ammonium chlorides and octyl phenoxy poly ethoxy ethanol showed good germicidal and spermicidal activities. Different phospholipids were evaluated for antibacterial,}
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antifungal, spermicidal and virucidal activities. Cellulose sulfate was reported to show both antimicrobial and spermicidal activities. Acyl Carnitine analogs showed spermicidal activity along with microbial and anti-HIV activities in in-vitro studies [3-6]. Nisin is well known class I bacteriocin produced by Lactococcus lactis subsp. lactis antimicrobial peptide showed spermicidal activity and could serve as a safe vaginal contraceptive for future therapeutic interventions in STIs [7]. Bactericidal ointment containing aloe and Benzalkonium chloride is used for killing AIDS virus and sperms and prevention of sexual transmitted diseases [8].

**Surfactants:** Agents capable of interacting with the lipoprotic membrane of spermatozoa include nonoxynol-9 (6), octoxynol-9 (7), dodecaethylene glycol monolaurate, methoxypolyoxyethylene glycol 550 laurate, menfegol, laureth 10S that have been approved by FDA [9].

![Nonoxynol-9](image1)  
![Octoxynol-9](image2)

However, only nonoxynol-9 and lesser extent octoxynol-9 are commercially exploited spermicides presently available. Though the anti HIV efficacy of nonoxynol-9 has been demonstrated in-vitro, it has no effect on transmission HIV/AIDS and STD infections like zidovudine [10]. Further, this is coupled with side effects such as vaginal disorders, cervicites, restriction of spermicidal action to vagina and not to cervix, pH dependency, massive nature and inability to maintain a uniform concentration of spermicide for long time which has limited use of nonoxynol-9.

Two saponins and flavonoids isolated from berries of *Phytolaccadioica L.* showed spermicidal activity [11]. A new formulation of Vaginal Suppository called “Long Acting Sustained Release of Spermicide” (LASRS) showed antimicrobial and spermicidal activities. Mono and diiodinated nonoxynol-9 derivatives were prepared and tested for spermicidal activity. Vanadocene dithiocarbimates (VDDTC, 8) has the most potent and stable spermicidal activity and may have clinically used as vaginal spermicidal contraceptive [14-16].

![Vanadocene dithiocarbimates](image3)

GM-144, a novel lipophillic vaginal contraceptive gel-microemulsion was formulated [17]. Di- and tri-hydroxylated cationic surfactants show promise as inexpensive topical contraceptive microbicides [18].

5. Acrosin Inhibitors: The most thoroughly studied acrosin inhibitors include 4-guanidinobenzoates and gossypol (9). 2-carbomethoxy-4-guanidino benzoate has been found to be most effective [12-13, 19]. Trihydroxy naphthalene (10) derivatives and its analogs were synthesized and showed activity similar to that of gossypol [19].

6.

Cysteamine, Phosphocysteamine (11) showed spermicidal activity along with Acrosin inhibitory activity. The non-immunogenic peptides derived from Zona Pellucida glycoproteins showed spermicidal activity in-vitro without inducing acrosome reaction in capacitated sperm [21-22].

5. Natural products: Several natural products have been evaluated for their spermicidal efficacy. These include polyphenolic compounds from plants alkaloids, magainins. Allitrudum an active principle of garlic showed complete immobilization of human spermatozoa at the 7.5mg/mL dose in-vitro. It had no bacteriostatic action on the lactic acid bacilli, so it would not interfere with the growth of the bacilli in the vagina [23-24, 27, 39]. Nepalins 1, 2 and 3 triglycerides from Hedera nepalensis K.koch showed spermicidal activity at 0.5, 0.25 and 0.125% respectively. Three new alkaloids were isolated from a Chinese plant Melodinus Fusiformis in which two showed significant spermatocidal and antitumor activity. Salannin (12), a limonoid bitter principle of the seed oil of Azadirachta indica, showed antiulcer, antibacterial and spermicidal activities [40-42].
In vitro study of pongamia seed oil from *Pongamia glabra* showed strong spermicidal activity [43]. Curcumin, a plant-derived diferuloylmethane (13) compound has selective sperm immobilizing effect in addition to a previously studied anti-HIV activity. This compound may have potential clinical application as a novel intra-vaginal spermicidal agent for contraception and HIV prevention [44].

Various forms of sphorolipids (14) produced by *Candida bombicola* showed spermicidal and virucidal activities [45].

6. Selective Serotonin Reuptake Inhibitors (SSRIs):
Paroxetine (arylmetharylxyloxy piperidine) and fluoxetine (aryloxyphenylpropylamine) which are Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants bind with neuronal 5-HT transporter through sulfhydryl group. They have been recently reported as non-detergent
spermicides. Other SSRIs which also shows non-detergent spermicidal activities are fluoxamine maleate, citalopram hydrobromide, and sertraline hydrochloride [9-10].

7. Miscellaneous compounds: most of synthetic compounds that have been evaluated for their spermicidal efficacy are substituted imidazoles, acrylophenones, benzophenones, parabens, mixture of betaine and amine oxides, urea, hydrogen peroxide, mandelic acid, citric acid, malonic acid, maleic acid, caffeic acid, chlorpromazine and phenoxybenzamine. New structural steroid type ring systems of benzthiadiazolones (15) showed good spermicidal activities [46-53].

New indolyl phthalazinones and phthalazine derivatives showed marked spermicidal activity, which was ten times that of N-9 [54]. 1,4-naphthaquinone was capable of generating reactive oxygen species (ROS) showed spermicidal and antimicrobial activities [55]. Promethazine hydrochloride (16) showed spermicidal activity at 0.4mg/mL concentration, which is more effective than Propranolol on human sperm [56].
Dihydro Alkoxyl Oxy pyrimidine [57] (DABO, 18) derivatives exhibited spermicidal activity as well as antiviral activity [58]. Acid form is an acid buffering vaginal formulation that maintains the acidic vaginal pH below 5.0 when ejaculate is deposited in the vagina or when a vaginal infection is present [59]. The Na⁺-Ca²⁺ exchanger and Ca²⁺-ATPase pumps reported to be present on the sperm membrane are responsible for maintaining the intracellular Ca²⁺ concentration that is involved in regulation of sperm function. 2', 4'-dichlorobenzamil hydrochloride (benzamil) (18), a Na⁺-Ca²⁺ exchange inhibitor showed spermicidal activity [60].

AZT derivatives showed spermicidal and anti-viral activity. Octyl-D-glucopyranoside (OGP) can immobilize and kill the sperms depending on concentration. Cyclohexenyl thiourea (CHET, 19) non-nucleoside inhibitors (NNIs) of HIV-1 reverse transcriptase (RT) derivatives showed clinical potential as anti HIV spermicides [61-64].

Activated Carbon, as well as compositions and kits comprising the same, are effective for preventing pregnancy and sexually transmitted diseases including HIV [65]. Metronidazole was
formulated in a concentration of 5% as an acid gel, which showed instant immobilization, and death of all sperms within 30sec. WHI-05 (5-bromo-6-methoxy-5,6-dihydro-3-azido thymidine-5-(p-methoxy phenyl) methoxy alaninyl phosphate, is a highly promising anti-viral and spermicidal agent. N-[2-(1-cyclo hexenyl) ethyl]-N-[2-(5-bromopyridyl)]-thio-urea (PHI-346) was studied as novel broad spectrum anti-HIV and spermicidal agent. OxoVanadium (V) complexes (20) with thiourea non-nucleoside inhibitors of HIV-1 reverse transcriptase showed potent dual anti-HIV and spermicidal activities [66-69].

Formulations containing at least one 5-alkyl resorc inol and Cannabinoids or both were useful as barrier contraceptives. Niphensamide is hopeful to become a safe, highly effective, inexpensive, convenient and new contraceptive with anti-infectious activity. Hexahydro indenopyridines (21) were synthesized as spermicides and antifungals [70-72].

Calcium hydroxide, Magnesium hydroxide and Aluminum hydroxide were formulated into gel form and used as contraceptive and antiviral powder. 4-[3-(di-alkylamino/ heterocyclic amino)-2-methylene-1-oxo-prop-1-yl]-1-O-[3-(heterocyclic amino / dialkyl amino)-2-hydroxypropyl] thymols (22) and their salts were prepared as potential vaginal contraceptive agents [73-74].
The spermicides in current use:
The great majority of vaginal contraceptive preparations that are available throughout the world rely on surfactants as the spermicidal agent. The most commonly used compound is nonoxynol-9. Other spermicidal products use either the structurally related compound octoxynol, or an alternative type of non-ionic surfactant, p-di-isobutyl-phenoxypolyethoxyethanol.

Surfactants have a common mode of spermicidal action. Nonoxynol-9 compound is spermicidal by virtue of its detergent action on the lipid components of the membranes of the mid-piece and tail regions of the spermatozoa, resulting in the rapid disruption of the membranes and loss of motility [75]. This mechanism is not selective and any unprotected lipoprotein membrane will be susceptible to disruption, including those of vaginal organisms. In addition to the direct detergent action, a cationic structure could have enhanced bactericidal lysis as the surfactant would be attracted or bound to the acidic components that are present in, or associated with, the bacterial wall, eg sialic or teichoic acid. Furthermore, it was proposed those non-ionic surfactants that have ether or amide linkages between the hydrophobic and hydrophilic domains of the molecule could have a virucidal action by virtue of their ability to dissolve the lipid components of the viral envelope. This prediction was made after the observed destruction of the envelope of herpes virus after in vitro exposure to nonoxynol-9 [76]. Many authors have been suggested that nonoxynol-9 may have role to play in the regulation of transmission of herpes virus during intercourse [77-78].

The restriction of the spread of STDs by spermicides was reported in 1972, when it was shown that Treponema pallidum, Neisseria gonorrhoea, Trichomonas vaginalis and Candida albicans were inactivated by exposure in-vitro to the levels of non-ionic surfactant spermicides that could be expected to be present in the vagina during intercourse when a spermicide was used [79]. This has been supported by other studies of women at high risk of STD infection, when the rate of reinfection was drastically reduced if a spermicide and condoms were used [80-81]. Subsequently it has been shown that nonoxynol-9 has activity against a wide range of bacterial and parasite-associated STDs; activity against viral infections has been demonstrated only in-vitro [83]. Nonoxynol-9 inactivate both cell based & free virus in-vitro, at concentrations well below those expected to be present in the vagina when a spermicide is used [84]. It is important to note that no data exist to show that spermicides are active against HIV in vivo except condoms [85].

Various factors that must be considered while assessing the use of spermicides-
The use of spermicides against STDs relates to their antiseptic action in-vitro. This approach should not be considered against the possible attenuation of the antiseptic activity by its dilution.

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R1=R2=R3=R4= Alkyl group

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on the male and female secretions, its speed of action, binding of the spermicide to proteins, or possible pH dependence of its action under the conditions that exist in the vagina during intercourse. The major disadvantage of Nonoxynol-9 is that it lacks entry into cervical mucus at the concentrations that would be present vaginally after the use of spermicides [86-87]. The rate of penetration of a spermicide into the genital tract is an important consideration in the prevention of infection.

1. Evidence exists showing that high levels of nonoxynol-9 cause lesions and severe ulceration of the vaginal epithelium of laboratory animals [88-89]. The adverse vaginal reaction to spermicides appears to be dose related, the usual rate of use being about 100 mg of surfactant at coitus. This level is, however, about 30 times greater than the ED$_{100}$ (the lowest concentration of nonoxynol-9 in semen in vitro, that results in 100% loss of motility 1min after contact), which has been shown to be in the region of 0.3mg/ml [90]. This has been seen that the damage to the epithelium would enhance the entry of STDs. Furthermore, damage to the epithelium of this sort could lead to increased numbers of T-lymphocytes and macrophages in the vagina which could increase the risk of infection by HIV. Indeed there is some evidence to support this suggestion. Some of the women used nonoxynol-9-containing sponges, a significantly higher rate of genital ulceration and HIV seroconversion was found with those not using nonoxynol-9 and it is possible that the abrasive action of the sponge was an important factor in these findings [91].

2. The use of spermicides as prophylaxis for STD is the effect of these compounds on the normal microbial species in the vagina. As spermicides have a degree of bactericidal action. There is a reported spectrum of sensitivity of the vaginal flora to nonoxynol-9; many of the species of Lactobacilli that are found in the vagina are susceptible to nonoxynol-9 after extended contact time in-vitro [92].

3. Nonoxynol-9 increases the risk of urinary tract infections, vulvovaginal candidiasis, and genital ulcers. N-9 may increase the risk of HIV transmission, perhaps by initiating interleukin-1-mediated NF-kB activation, which leads to cytokine-induced recruitment of HIV-1 host cells and increased HIV-1 replication. N-9, a mixture of oligomers may violate future federal regulations; pure compounds or mixtures whose individual components have safety standards will become the norm. Furthermore, the breakdown products of N-9 pose serious health and environmental risks [93-104].

Thus none of the agents, synthetic or natural is known so far having spermicidal activity fulfill the essential requirement of a modern 21st century spermicide i.e., having action against both the spermatozoa and the organisms causing STD and AIDS without affecting the vaginal flora. The requirement for a dual-function spermicides are given below:

- Potent spermicidal activity.
- Efficacy against HIV infection
- Effective as antibacterial and antifungal agent
- Nontoxic to vaginal flora
- Minimal membrane toxicity

In humans, this process is regulated by oxidoreduction reactions. Sperm capacitation is associated with a low production of reactive oxygen species (ROS) and a strong time-dependent increase in sperm membrane sulfhydryl groups. Sulfhydryl groups of sperm membrane proteins maintain a dynamic equilibrium with their disulfides counterparts. Oxidation of sulfhydryl
groups is associated with the initiation of fertilizing ability of spermatozoa. In rat epididymis, caput ligation caused an oxidation of sperm sulfhydryl groups triggering an early maturation of the gametes as evidenced by the acquisition of motility and of a partial increase in fertilizing ability [105-111].

Sulfhydryl groups of the sperm membrane play a very important role in sperm motility and metabolism and evidence is also available for the involvement of these surface thiols in normal sperm functioning [112-113]. The loss of sperm surface thiol groups and the augmented production of superoxide anion radical were stated to be the reason for the loss of motility [114]. The sulfhydryl blocking properties of both copper and cobalt is utilized to study role of sulfhydryl groups in sperm membrane modulation. Several reports show that a sulfhydryl group plays important role in sperm membrane modulation and as a marker for fertility assessment [115].

Membrane integrity and its proper functioning are characteristics of the sperm membrane including cellular recognition and information transduction during cell-cell interaction. Changes in composition of fatty acid of membranes as well as the amount of individual sterols, account for the change in fluidity. Normal spermatozoa are reported to show high membrane fluidity [116]. Therefore it is evident that membrane fluidity is an important factor for sperm functions. Lipid peroxidation plays a crucial role in inducing membrane fluidity [117].

It has been seen that copper containing antifertility devices (Copper-T) act via production of toxic oxygen radical species including hydroxyl and superoxide anion radical and these radical species are known to induce membrane fluidity via lipid peroxidation [118]. But, contrary to the above statement it was found that blocking of sulfhydryl groups by copper and cobalt inhibits lipid peroxidation in normal spermatozoa and treatment of oligospermic samples with pentoxifylline increases lipid peroxidation [115].

According to the various conditions (medium, stimulant, etc.) used by different researchers, O$_2^{*2}$, H$_2$O$_2$, or both of these oxidants induce human sperm capacitation. These observations converge to emphasize again the concept that sperm capacitation is part of an oxidative process. However, the extracellular sperm membrane target for O$_2^{*2}$ during capacitation remains elusive [119-120].

**CONCLUSION**

The present review article strongly suggest that the sulfhydryl-disulfide pair is involved in the regulation of human sperm capacitation and the associated O$_2^{*2}$ generation. The reversibility of oxidoreduction reactions involving sulfhydryl and disulfide groups and the possible shuttle between these two forms are compatible with the reversibility of the capacitation process. In addition, the fine control of the sulfhydryl-disulfide pair could offer a mechanism by which sperm capacitation would be prevented until appropriate conditions (location in the female genital tract, timing, etc.) occur and then be induced. However, the factors involved in this fine control of the sulfhydryl-disulfide pair appear complex and multifactorial and may involve many parallel or associated signal transduction pathways leading to sperm capacitation. As it is suggested that sperm membrane sulfhydryl groups are important entities of the membrane and can be used as a tool for infertility assessment in unexplained male infertility and can be targeted for contraceptive research, we wanted to explore the sulfhydryl-binding agents. Hydrogen
peroxide, o-iodobenzoate, several hydroquinones, phenyl mercuric acid, Maleimide derivatives like compounds are reported for their spermicidal activity and all compounds show the thiol-disulfide conversion in mode of action.

N-Ethylmaleimide, a sulfhydryl-selective alkylating agent and its derivatives have been found to possess spermicidal activities, which is attributed to their interaction with the sulfhydryl groups present over sperm cell membrane. Since binding to sulfhydryl groups of sperm membrane is important for the spermicidal activity, and paroxetine hydrochloride, a SSRI antidepressant, is known to bind with serotonin transporters by interacting with sulfhydryl groups; it was suspected that SSRIs could possess spermicidal activity. Further, tricyclic antidepressants, Amtriptylin and Imipramine have been shown to possess sperm immobilizing activity and certain SSRI antidepressants have been found to possess antifungal activity. Additionally, serotonin functions as a neurotransmitter in brain, as well as in a number of other tissues including testis, where it exerts effect by binding to cell surface receptors.

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