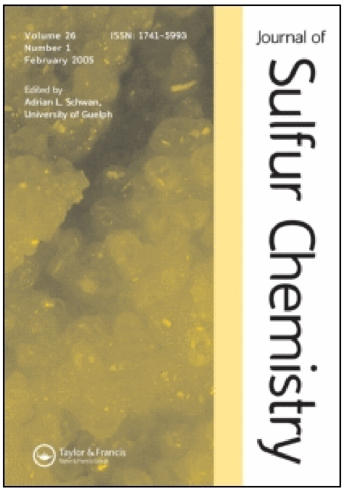

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THE BIOLOGICAL ACTIVITY OF SELENIUM SULFIDE

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The history of selenium sulfide and its chemical nature as a discrete compound are discussed together with its uses within the medical field of dermatology. Evidence for its effects on biological systems are presented and potential mechanisms of action via its antimicrobial activity, effects on cell growth and its role as a catalyst in the enhancement of the activity of sulfur are critically reviewed.

Key words: antimicrobial, biochemistry, cell growth, dermatological, selenium sulfide, toxicity.

CONTENTS

1. INTRODUCTION

Selenium has enjoyed an aeonial association with sulfur. It has been found admixed, in small proportions, with sulfur deposits taken from many volcanic

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regions of the earth's crust.[1-3] Such seleniferous impurities may have been responsible for the alleged "red sulfur" (*sulfur rubeum*) found lining the inner walls of chambers employed for the vaporisation and purification of crude sulfur,[4] thereby leading to the inadvertent documentation of this unknown element as early as the fourteenth century. Similar observations may have gone unreported for many years as the production of both sulfurous and sulfuric acid, valuable liquids whose manufacture requires the roasting of sulfur ores, may have been known to the Arabian peoples as early as the eighth century A.D.[4]

It was during such a process that sulfur finally relinquished its hidden companion. The Swedish sulfuric acid works in Gripsholm obtained the sulfur dioxide it required for its lead chamber process by roasting seleniferous copper pyrites mined in Falun. The use of this ore, unlike several others, led to the deposition of red-brown muds within the lead chambers. The belief that these sediments could provide a cheaper source of tellurium, discovered thirty-five years earlier, led Berzelius and Gahn (1817) to inadvertently isolate a previously unknown substance.[5,6] The name selenium, derived from the Greek moon goddess, was chosen for the new element to signify its close chemical (and physical) association with tellurium, itself being deified previously via Tellus, the Roman goddess of the earth.

2. THE NATURE OF SELENIUM SULFIDE

In the years following the discovery of selenium intensive research revealed many of the physical and chemical properties of this new element. Amidst the plethora of information gathered it was shown that sulfur and selenium could be fused together in all proportions. However, these initial reports assumed that two discrete chemical compounds, selenium disulfide and selenium trisulfide, were formed, partly by analogy with the oxides.[5-9] Doubts were cast when further work suggested that even with slow cooling the mixtures solidified into an amorphous form. When the proportion of selenium was high crystallization could be achieved, but even then it was necessary to heat the fusion for many hours at temperatures near the melting point of selenium. Any crystalline products that were obtained were presumed to contain only mixed crystals and no evidence for the formation of a compound was observed.[10]

So the situation remained up to the 1950's. Investigations had continued but it was still not certain if the different crystalline phases containing sulfur and selenium in varying proportions were true chemical compounds with covalent sulfur-selenium bonds or simply mixed crystals consisting of discrete eight-membered sulfur and selenium ring molecules.[11]

Examination of the vapour phase above molten mixtures of sulfur and selenium showed that the relative volatilities of the elements, and the pressure, composition and component densities of the vapours were not those theoretically expected from a simple mix and suggested the existence of covalent compounds.[12-16] X-Ray diffraction studies of such melts clearly showed the presence of crystalline selenium monosulfide (interestingly, the only sulfide of selenium whose existence as a chemical compound was regarded as established over a century ago[17]), but the remaining material consisted of solid solutions of sulfur and selenium in an amorphous form.[18] Further investigation revealed that the sulfur and selenium existed within these melts as covalently linked compounds with the general formula Se_nS_{8-n}.[19,20]

Extensive studies on benzene recrystallization products obtained from cooled molten mixtures have provided 18 different fractions, coloured from pale yellow to deep red, with selenium contents from 3.2 to 52.1 mol%, suggesting compositions between S_8 and Se_4S_4. Mass spectrometry confirmed the presence of all species of the Se_nS_{8-n} range.[21] However, even gentle heating of such samples may initiate disproportionation reactions and the measured composition of the vapour does not necessarily reflect the initial composition of the solid material under investigation.

Nevertheless, detailed structure determinations have confirmed that in all such products the crystal lattices are composed of eight-membered crown-shaped molecules analogous to S_8 and Se_8 rings. The structures were found to be disordered with sulfur and selenium distributed statistically over the atomic sites and several different Se_nS_{8-n} molecules within the same lattice.[22–26] Twelve-membered molecules of the general formula Se_nS_{12-n} have also been investigated and their molecular geometry resembles that of S_{12} rings.[27] Other ring sizes (6- and 7-membered) have also been proposed.[28]

A similar situation exists for selenium sulfides prepared by different chemical routes other than elemental fusions. The passing of hydrogen sulfide through selenous acid yields a yellow precipitate of empirical composition SeS_2, which has been regarded as a discrete compound, selenium disulfide.[5–9] However, the suspicion that something was amiss arose following its recrystallization from carbon disulfide. A product with an increased proportion of selenium and a molecular formula corresponding to $Se_{3.3}S_{4.7}$ was thus obtained, suggesting the removal of sulfur into the solvent.[29] This was confirmed over a century later when this product, together with two others of empirical formula $Se_{2.9}S_{5.1}$ and $Se_{4.7}S_{3.3}$, were detected during recrystallizations from an organic solvent extract of selenium disulfide. X-Ray diffraction data obtained from the products was consistent with the formation of cyclic eight-membered molecules, presumably of the generally accepted formula Se_nS_{8-n}.[23]

It can be concluded that stoichiometrically pure selenium sulfides appear elusive and cannot be obtained from molten mixtures of the elements. Specific chemical reactions may yield such compounds (e.g. Se_2S from sulfur dioxide and hydrogen selenide[29] or SeS_3 from selenium dioxide and *N*-benzylthiamides[30]) but there are still doubts which need to be satisfied.

The selenium sulfide preparations employed therapeutically arise from the fusion of sulfur and selenium in a molar ratio of 2:1 and as such are commonly termed "selenium disulfide." This bright orange to reddish-brown powder, insoluble in water and possessing a faint odour of hydrogen sulfide, is generally considered as consisting of a mixture of crystalline selenium monosulfide and solid solutions of sulfur and selenium in an amorphous form.[18] The product is commercially available as a shampoo containing either 1% or 2.5% active ingredient, suspended in a scented detergent vehicle, as a cream formulation containing 2.5% selenium sulfide, or as detergent bars containing between 0.1% and 5% of the compound as a transparent dispersion.

3. THERAPEUTIC APPLICATION

It is in the treatment of skin disorders that selenium sulfide has found its major therapeutic application (Table 1). This group of conditions, described by differing medical terminology, are characterised mainly by inflammation of the skin (dermatitis) or hair follicles (folliculitis), an overaction of the sebaceous glands, and varying degrees of exfoliation of the epidermis (pityriasis). A common causative factor for all these problems remains elusive, but fungal infections are thought to play a critical role in the majority of these ailments.

Pityriasis versicolor (tinea versicolor) was first recognised as being of fungal aetiology in 1846 and in the following few years the fungus was described and named *Microsporium furfur.*[31] Confusion has since arisen owing to further observations which have necessitated several reclassifications. The genus of the fungus was altered to *Malassezia* in 1889 and evidence has slowly accumulated that *Malassezia furfur* and the independently identified *Pityrosporum orbiculare* are the same organism with the previously discrete *Pityrosporum ovale* probably representing an additional and different morphological form.[32–34] The name *Malassezia furfur* is still used and considered by some to be the correct designation for a combination of *Pityrosporium orbiculare* and *Pityrosporium ovale* (which they regard as potentially separate organisms), suggesting that it specifically describes the filamentous form of these yeasts.[35] This fungus species, which is a normal component of the human cutaneous flora, can change from a saprophytic yeast to an invasive pathogenic mycelium under the influence of several, as yet unresolved factors.[34,36]

Being cognisant of these microbiological interrelationships it becomes evident from the literature that *Pityrosporum* species have been implicated as potential causative factors in not only pityriasis versicolor,[37–39] but also pityrosporum folliculitis,[40,41] psoriasis,[42] seborrheic dermatitis,[43,44] transient acantholytic dermato-

TABLE 1 Selenium sulfide has found therapeutic application in the treatment of the following disorders

congruent and reticulated papillomatosis of Gougerot & Carteaud
dandruff (pityriasis sicca)
pityriasis versicolor
pityrosporum folliculitis
psoriasis
seborrheic dermatitis
tinea capitis
transient acantholytic dermatosis (Grover's disease)

sis,[45] and "congruent and reticulated papillomatosis of Gougerot and Carteaud."[46–48] However, their precise role, which may sometimes be opportunistic and following other initial events, is still controversial, especially in the latter papillomatous condition.

Tinea capitis (scalp ringworm) is known to be caused by other fungal infections including *Trichophyton tonsurans, Trichophyton violaceum*, and *Microsporum audouni*.[49,50] A related fungus, *Microsporum canis*, can be contracted from infected domestic cats.[51]

Dandruff is a relatively familiar and common complaint of uncertain aetiology. Sometimes a preponderance of yeast cells or pseudo-hyphae can be detected on the discarded white scales and the scalp suggesting a fungal causation, and this may be the more common operative aetiological factor. However, at other times clumps of nucleated keratinocytes are observed, suggesting premature and exaggerated exfoliation, reminiscent of seborrheic dermatitis, psoriasis, or ichthyosis. Whether these two observations are linked and fungal infection can increase epidermal turnover is not known. The influence of other factors is evident, however, as the symptom may become more pronounced in certain disease states.[43,52–54]

4. TOXICITY AND ADVERSE REACTIONS

Despite the general opinion in the literature that selenium compounds are toxic, selenium sulfide appears relatively innocuous. This is presumably on account of its low aqueous solubility ($<$ 1 mg/ml, 0.01 M HCl) resulting in very poor systemic absorption following its topical (man) or oral (mouse, dog) administration.[55–58] This is reflected in the oral LD_{50} values obtained for rodents (rat, mouse) which are at least an order of magnitude greater than those obtained for the water soluble (700 mg/ml, 0.01 M HCl) and toxic sodium selenite.[55,56] However, one study has reported increased urine selenium levels in patients after application of selenium sulfide lotion and warns that prolonged treatment may lead to possible, but unspecified, health hazards.[59]

Little acute toxicity data is available for man as the therapeutic formulation of selenium sulfide with detergents has surreptitiously thwarted suicide attempts by making the product a fairly effective emetic. Treatment of cell cultures (human skin, chick embryo spleen) with an aqueous suspension of selenium sulfide has shown that it is no more toxic than the detergent vehicle employed in shampoos.[60] However, superficial inflammation of the cornea (keratitis) was observed after application of the compound to the conjuctival sacs of rabbits, this response appearing to be initiated almost immediately.[61] Studies have suggested that the oral administration of selenium sulfide to rats and female mice produced an increase in hepatocellular carcinomas and adenomas. Female mice also showed an increase in lung tumours (adenoma and carcinoma of alveoli/brochioles).[62] The results obtained from several short term *in vitro* tests for mutagenesis, which purport to predict mammalian carcinogenesis, are less convincing. Whilst the compound was mutagenic to *Salmonella*, (bacterial test for gene mutation)[63] inferences made from the measurement of unscheduled DNA synthesis in rat hepatocytes (a test for repairable DNA damage) as a response to the presence of selenium sulfide have been ambiguous.[64] However, the compound, formulated as a therapeutic shampoo, did not produce dermal tumours when applied topically to mice and has subsequently been regarded as safe for human use.[65,66] In addition, the World Health Organisation had earlier concluded that a comprehensive assessment of available data had provided no suggestion that selenium was carcinogenic to man.[67]

Adverse reactions to the use of selenium sulfide products are few. Prolonged skin contact may result in itching and cutaneous eruptions (dermatitis venenata) especially in patients with dry ichthyotic skin.[68] However, other authors report no cases of sensitization to selenium sulfide during four years of clinical application.[60] An orange-brown discolouration of the nails and light (fair or grey) hair may also occur[69,70] and topical application during the treatment of pityriasis versicolor has led to the suppression of lactation.[68]

Several scattered reports have intimated a diffuse hair loss after the use of selenium sulfide shampoos[71] and when this substance was applied to the skin of guinea pigs there was a significant increase in telogenic (resting phase) hair.[72] An abnormal development (dysplasia) of hair roots has been observed following lengthy exposure (9 hours) of the human scalp to selenium sulfide shampoo.[73] However, other investigators have reported that exposure over several months to selenium sulfide preparations during normal hair washing procedures caused no demonstrable damage to hair roots in the healthy human scalp.[74] It appears that such problems may only arise after an intense and prolonged exposure. Nevertheless, one of the characteristics believed to enhance the efficacy of selenium sulfide is that it has been shown to be deposited on the scalp surface during shampooing and remains there, not being removed during the normal rinsing procedure.[50,75] The degree of subsequent scalp penetration presumably influences its adverse effects on hair growth.

Other studies have shown that treatment with such shampoos can cause an increase in sebaceous gland secretion in man leading to an excessive oiliness of the scalp after three to four weeks of use.[44,70,76,77] Further directed investigations have proven that local application of selenium sulfide leads to an increase in the size of the sebaceous glands both in guinea pigs and hamsters.[78,79]

5. BIOLOGICAL ACTIVITY

5.1. *Antimicrobial Activity*

Selenium sulfide, both in aqueous suspension and formulated as a shampoo, has been shown to possess antimicrobial activity against species belonging to several different genera of fungi and bacteria (Table 2).[18,80–85] It has even been suggested that selenium sulfide should be used to treat products before human consumption to offset potential microbial decay within foods and beverages.[86]

TABLE 2 Selenium sulfide has shown microbial activity against organisms within the following genera

Fungi	Bacteria
Aspergillus	Leptospira
Candida (Monilia)	Micrococcus
Chaetomium	Staphylococcus
Microsporum (Microsporon)	
Myrothecium	
Pityrosporum	
Trichophyton	

Several studies have shown that the compound inhibited fungal growth and that the activity was apparently fungicidal in nature and not fungistatic, unlike similar dermatological agents such as coal tar.[50,81] It has been proposed that its mode of action may be via interference with normal fungal sulfur metabolism. An irreversible polymerisation of free thiol groups to form stable polysulfide bonds may occur within the fungal cell walls, thereby preventing cell expansion and making further cell division impossible.[87] This restrictive fungistatic effect presumably leads to cell death via gross functional disruption and eventual lysis.

5.2. *Effects on Cell Growth*

During clinical investigations the use of selenium sulfide shampoos was shown to be able to halve the exfoliation rate of keratinized cells from dandruff prone scalps (corneocyte count). It was suggested that the chemical exerted a cytostatic effect, decreasing the rate at which these horny cells were manufactured by the epidermis.[88] Such inhibitory effects on epidermopoiesis have been advocated by other workers who have proposed that selenium sulfide ions may block the enzyme systems involved in the growth of epidermal tissue and thereby decreasing cell turnover.[45,89]

It has been postulated that the detergent in shampoos can release previously unreactive thiol groups which may then be inactivated by selenium sulfide.[18,90,91] Access to the thiol groups of cellular enzyme systems is doubtful and any disruption is presumably limited to cross linkages within the keratin molecule which are in the upper layers of the epidermis.

Nevertheless, cases of apparent poisoning with signs and symptoms similar to mild hydrogen sulfide intoxication have been reported following the use of sulfur-containing ointments.[92] The application of such ointments to the skin has led to the absorption of finely divided sulfur and its reduction to sulfide and hydrogensulfide ions either before, during, or after absorption.[93–95] An increase in the sulfur content of the blood has also been demonstrated following the dermal application of a sulfurated oil containing elemental sulfur.[96] Similarly, minute traces of selenium sulfide could likewise be absorbed through skin or hair follicles and be converted into selenide and sulfide ions with the former disrupting enzyme function.

Selenium has been shown to inhibit normal DNA synthesis in mouse mammary epithelial cells.[97] Recent investigations involving selenium trisulfide have indicated that during nucleic acid transcription the compound can associate with free RNA polymerase II, forming an inactive enzyme that is then unable to interact with the template DNA to form the required enzyme-DNA binary transcription complex. Thus, selenium trisulfide interferes at the initiation stage and subsequently has the effect of decreasing the number of transcription complexes which are active during elongation, with a resulting decrease in the overall rate of RNA synthesis. Although this is true with RNA polymerase II derived from wheat germ and HeLa cells (cultured human malignant cells from cervical carcinoma), complications arise with bacterial enzyme obtained from *Escherichia coli* where selenium trisulfide inhibits the elongation stage of the reaction, not the initiation process.[98,99] Such interactions could presumably be feasible for other selenium sulfur compounds possessing different stoichiometry.

In contrast, however, work on cells from the hamster sebaceous gland has indicated a shortening of the stationary (resting) phase of the cell cycle, an increase in thymidine uptake (DNA nucleoside) and an increase in overall mitotic rate (blocked at metaphase), all suggesting an increase, not a decrease, in the rate of cell turnover.[79] Conversely, percutaneous application of selenium sulfide to guinea pig skin increased the resting phase during hair growth.[72] How these apparent discrepancies can be reconciled is not yet clear.

5.3 *Enhancement of the Activity of Sulfur*

Over sixty years ago selenium sulfide was proffered as a suitable agent for the treatment of skin diseases, being particularly successful with previously recalcitrant cases of eczema. The reasoning behind this abstruse proposal, for this stable selenium sulfide was initially developed to detect leaks from mercury vapour turbines, was presumably that within this combination the sulfur moiety was in an extremely active form, and sulfur itself was known to possess fungicidal and therapeutic (keratolytic) properties. It was assumed that selenium only served as an activator and that the therapeutic activity resided with the sulfur.[100]

This view may contain a certain element of the truth. In its defence one report has emphasized several chemical facts of possible significance.[101] When combined with sulfur, selenium tremendously increases the activity of the former element. In the photovoltaic cell the addition of selenium greatly increases the photosensitivity of sulfur, selenium itself exhibiting photovoltaic and photoconductive activity.[102] The selenium present in selenium sulfide may simply act as an intramolecular catalyst, replacing part of the sulfur in ring molecules and making the sulfur a more effective therapeutic agent. As an interesting adjunct, cadmium sulfide (capsebon) has been used successfully to treat seborrheic dermatitis of the scalp. It appears as effective as selenium sulfide, but less irritating, perhaps suggesting a common activity within the sulfur moiety. However, cadmium has its own toxicity problems.

As previously implied, elemental sulfur has been shown to possess fungicidal, parasiticidal, germicidal and keratolytic properties which have been exploited for many years. The mechanism(s) underlying these actions of sulfur have resisted clarification, but it is thought unlikely that the element itself is biologically reactive and that it requires conversion to simple inorganic compounds before it can achieve activity.[103] It has been stated that sulfur must be converted to pentathionic acid ($H_2S_5O_6$) in order to exert its germicidal activity, and that this oxidation is presumably accomplished by the epidermal cells or by certain microorganisms when the element is applied to the skin.[104]

However, it has also been suggested that the mode of action of sulfur is "*perhaps more subtle than is usually supposed.*"[103] With selenium sulfide could it be that the sulfur moiety, made even more reactive by its close association with selenium, undergoes oxidation[104] or reduction[93–95] and that it is the act of transformation, a shift in electronic form, and not the inorganic product itself, which brings about coincidental and non-specific, but nevertheless deleterious consequencies to any living system in the immediate vicinity.

6. CLOSING REMARKS

Despite the many reports to the contrary, the beneficial actions of selenium sulfide are still under doubt. For example, advice given in recent editions of the British National Formulary, a text strongly recommended for medical practitioners within the UK, states that "*shampoos containing selenium sulphide are of no more value than other shampoos.*"[105] Such brusque disregard for any potentially beneficial effects, and the attitudes so created, have helped to decrease popularity and neutralise research desire. The evidence assembled within this review has demonstrated that selenium sulfide certainly has biological effects, but reveals that the underlying mechanism(s) of action have escaped explanation. Both selenium[106] and sulfur[103] have their own discrete interactions with biological systems. When presented as selenium sulfide we may be witnessing simply the additive and merged effects of these two elements or, more probably, a new property unique to this combination. The original suggestion[100] that the biological activity of sulfur is grossly enhanced by its intimate association with selenium is a strong candidate, but only further exploration will unravel this enigma.

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