Technical

The Potential Commercial Aspects of Gossypol[1]

R.J. Hron Sr., S.P. Koltun, J. Pominski and G. Abraham
Southern Regional Research Center, ARS/USDA, P.O. Box 19687, New Orleans, LA 70179

Gossypol, a yellow polyphenolic pigment contained in all plant parts of the predominant cotton cultivars, has been the source of practical as well as scientific interest for over a century. Recent changes in both cotton fiber and cottonseed products markets have focused renewed interest on potential alternate uses for fiber and seed and other products of cotton and for the gossypol contained in the seed. A review of the literature dealing with the potential commercial use of gossypol from 1886, when it was first isolated, until the present, is presented.

Examination of a recent catalog of a major chemical supplier (1) reveals approximately a twentyfold greater value per unit weight of gossypol as compared to the current price of gold. What is it about this commodity that commands such a high value? Gossypol was first isolated by Longmore in 1886 from soapstock obtained on refining cold-pressed cottonseed oil (2). Marchlewski purified it in 1899 by precipitating it from an ether solution using acetic acid to produce gossypolacetic acid (3). After isolating it, he named it gossypol based upon its vegetative family species gossypium and its polyphenolic chemical nature. Although cottonseed is the most familar source, gossypol has been found in the bark and flowers of the tropical tree, *Thespesia populinea* (4), common to Africa, Asia and the Pacific Islands, and in certain other members of the family *Malvaceae.* Okra, one of the staples of New Orleans creole cooking, also is a member of the same family and was reported to contain gossypol in its seeds (5,6). This was later shown by the use of chromatographic methods, to definitely not be gossypol; it may be degradation products of hydroxylated unsaturated fatty acid triglycerides reacting with the aniline used in the gossypol analysis (7).

The chemical structure of gossypol was first derived in 1938 by Adams and his students, who did extensive studies on its properties and reactions (8,9). Twenty years later Edwards confirmed Adams' structural formula by being the first to synthesize gossypol (10). Because of gossypol's uniqueness and challenging chemistry, it has been studied by many researchers since its discovery. This group includes many scientists at the Southern Regional Research Center (SRRC), who have done extensive research on all aspects of gossypol contained in cottonseed.

Although gossypol exists in all parts of the cotton plant, its containment within the pigment glands of the seed is of primary importance. Figure 1 is a cross section of a cottonseed showing the pigment glands scattered throughout. The glands range in size from 50 to 400 microns (11). Figure 2 shows what Boatner and her group of researchers at SRRC saw in 1947 when they contacted the glands with water. The glands immediately rupture and spew out their contents in the form of a suspension of 0.1- to 1.5-micron pigment spherules (12). Gossypol approximates 95% of the pigments contained in the gland and accounts for 39 to 50% of the total gland weight. Although Boatner and others have reported the presence of at least 15 other gossypol-like pigments existing in seed, there is some thought now, through the use of newer, sophisticated instruments, that most of them actually may be oxidation or condensation products of gossypol (13). The structural formulas for gossypol are shown in Figure 3. Gossypol is a very reactive, polymorphic compound that Adams and co-workers in 1938 found to exist in three tautomeric forms (8). The top aldehyde tautomer formula is the one generally used for gossypol, but gossypol actually exists in either of the two other tautomeric forms at the same time. The three forms are used as an explanation for its reactions as an aldehyde, hemiacetal and/or quinoid. Gossypol is soluble in many organic solvents but is insoluble in water and the low-boiling fraction of petroleum ether. Pure crystallized gossypol has been found to have distinct melting points depending upon the solvent used in its crystallization. Gossypol crystallized from ether melts at 184 C, crystals from chloroform melt at 199 C and crystals from Skelly-B, a high boiling petroleum ether, melt at 214 C (14). Reversible transformations of these tautomers can be shown by taking crystals formed from one of these solvents and redissolving and recrystallizing them from a different solvent. The resulting crystals now melt at a temperature corresponding to the new solvent. Although varying in melting points, all three crystals give the same chemical reactions. It would be logical to assume that there might be a relationship between the various crystal melting points and the various tautomeric forms, but no one has reported any such relationship.

The presence of gossypol in cottonseed has been a major economic problem to oil millers, but its high reactivity, especially with other seed components, is at times a partial asset. Such is the case where it has increased the costs of production by forcing a moist cook or other seed treatment in order to chemically bind free gossypol and reduce it to safe feeding levels for non-ruminants. It also has reduced the value of oil in the market place due to dark color which sometimes may be corrected by additional costly refining steps. Finally, it reduces the nutritive value of extracted meals, by reacting with lysine, the limiting essential amino acid in cottonseed, reducing its availability (15). Gossypol's toxicity to non-ruminants and its discoloration effect on hen's eggs for the most part can be negated by the conversion of free gossypol to the bound form and/or by the addition of iron salts (16).

The preparation of gossypol is a tedious and time-consuming operation. Separated pigment glands are probably the first choice as a starting raw material. One method of obtaining glands is by the gland flotation process, which was developed at SRRC by Boatner's group in 1946 (17). They found a density difference between glands, hulls and kernel tissue and capitalized on this difference by disintegrating dry cottonseed flakes in a slurry of hexane and various other solvents, like per-

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chlorethylene, trichlorethylene or carbon tetrachloride, mixed in a proportion to give a specific gravity of 1.378 g/cc. The glands float to the top and can be easily skimmed off. This separation can be made continuous to produce a solvent-washed concentrated gland fraction (18). The glands then can be extracted in a few minutes, under violent agitation, in a Waring blender using acetone. The mixture is filtered and the addition of glacial acetic acid to the filtrate produces a precipitate of gossypol-acetic acid. Hydrolysis of the precipitate produces pure gossypol at approximately a 65% yield of the original gossypol contained in the starting gland fraction (19).

Pons, of SRRC, in 1959 developed a method of obtaining pure gossypol from cottonseed gums acquired from water washing crude solvent extracted oil. Based on the laboratory results, a pilot plant process using 18.1-kg lots of gums was developed, a flowsheet of which is shown in Figure 4 (20). In this process, gums containing approximately 5% gossypol are refluxed with methyl ethyl ketone (MEK) containing phosphoric acid to hydrolyze bound gossypol pigments. The solution is cooled and two phases separated with most of the gossypol in the MEK phase. The MEK phase including washings is concentrated and, after the addition of acetic acid, crude gossypol acetic-acid is precipitated. The precipitate is filtered, washed with hexane, and then vacuum dried to produce 93% purity gossypol-acetic acid at approximately a 45% recovery rate. This equates to about 0.5 kg from 18.1 kg of starting gums. The gossypol-acetic acid can be further purified or pure gossypol can be obtained by hydrolysis as previously described. Koltun and co-workers followed up with a cost study which showed that pure gossypol could be obtained for $12.24/kg at 1958 prices or roughly $46/kg today (21). Twenty six kg of highly purified gossypol acetic acid has been produced at SRRC in our pilot plant. Most of it has been distributed to researchers all over the world, some of whom have been trying to find a productive use for the compound.

Starting with Kuhlmann in 1861, all of the early gossypol researchers including Longmore and Marchlewski thought they had an excellent use for gossypol and its various brightly colored derivatives as fabric dyes (2,22,23). None of their products, some of which were patented, were ever commercialized. This was possibly due to the known light sensitivity of gossypol and or the availability of cheaper and better dyes. The search for other uses was delayed while researchers concentrated on determining its structure and chemistry. Gossypol was reported to be one of the strongest antioxidants found in nature, but because of a belief in its toxicity, it has never found a use in food products even though Hove and Hove reported that in non-harmful concentrations, it is still a very effective antioxidant (24,25). The Japanese in 1954 reported on its use as a stabilizer for vitamin A in products (26). Royce in 1933 reported on the possible use of gossypol as an antioxidant in the petroleum and rubber industries (27). This was followed up by Piotrovskii and co-workers, who in 1975 reported that a derivative of gossypol could be used as a stabilizer for synthetic rubbers (28). Researchers in the USSR have also done extensive research on all aspects of gossypol during the last 50 years and more recently have found gossypol to be an effective antioxidant-stabilizer for PVC and polypropylene (29–32). They also have reported on its use as a stabilizer in cement mixtures for road foundations and in spackling, where it increases the life and cold resistance and decreases water absorption (33,34). There are also numerous USSR references to the use of gossypol in drilling muds used in the petroleum industry. Here it is

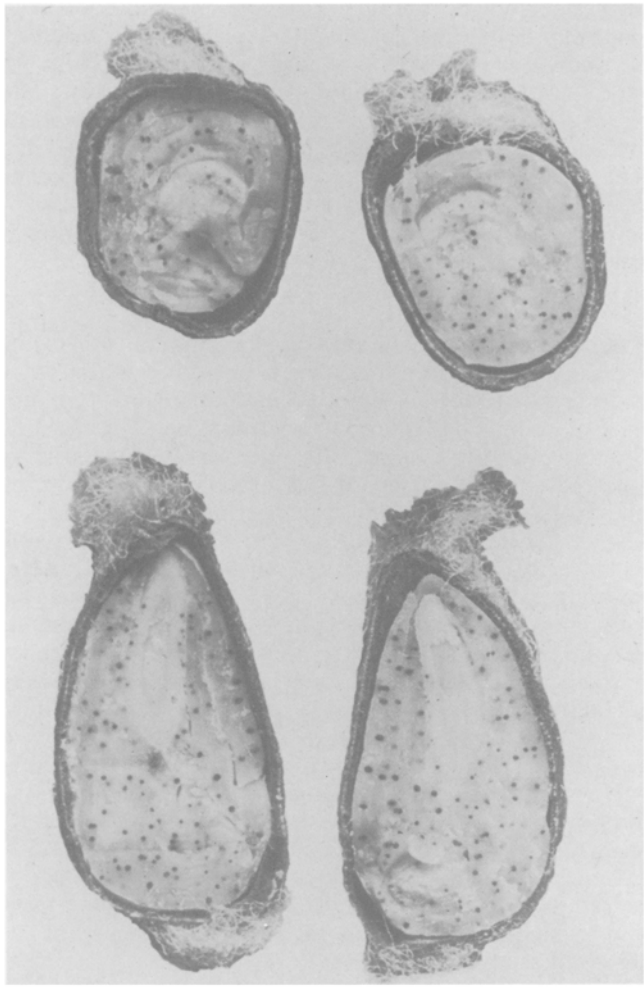


FIG. 1. Longitudinal and axial cross sections of cottonseed showing distribution of gossypol-containing pigment glands.

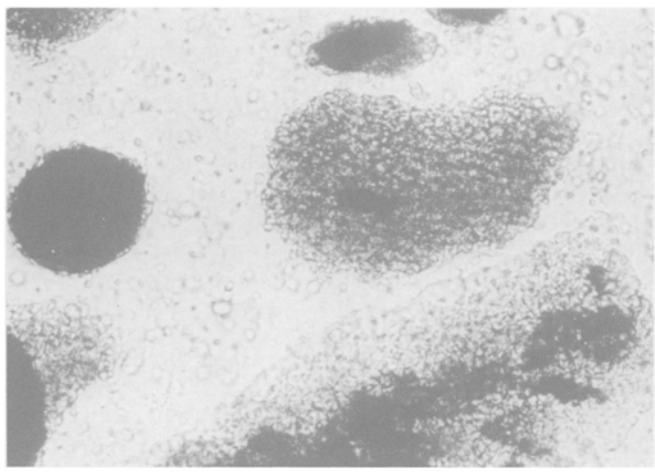
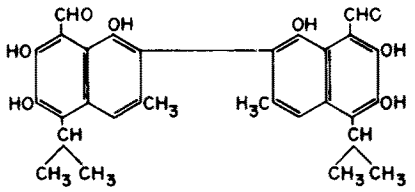


FIG. 2. Pigment spherules streaming out of ruptured pigment glands.



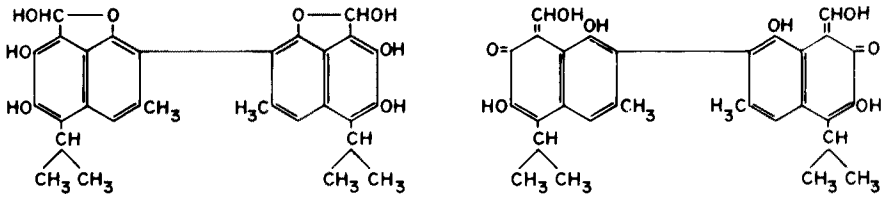


FIG. 3. Structural formulas for the various tautomeric forms of gossypol.

reported to increase heat stability and suppress viscosity and water loss (35–37). Samples of gossypol sent to the Naval Weapons Center in China Lake, California in the 1970's were instrumental in the issuance of a patent for the use of gossypol to extend batch mixing time and act as an antioxidant in rocket propellant formulations (38 and J. Braun, personal communication, 1973). They also found that gossypol chelated with iron was effective in preventing rusting, and some of its derivatives found by researchers were effective as qualitative and quantitative reagents in the determination of cobalt, nickel, copper, zinc, iron, tin, antimony, niobium, molybdenum, vanadium and uranium (39).

The early investigators of gossypol rightly suggested its possible use in pharmaceuticals, and it is here where it has gained the most attention. One of the earliest reported medical uses for gossypol occurred in 1872 when Wayne described his use of a cotton-root bark extract (rich in gossypol) to promote or assist menstrual flow and to prevent hemorrhaging (40). Recently Murthy and coworkers discovered that gossypol effectively inhibits egg implantation (41). Although no one to date has associated these two findings, perhaps researchers should investigate other folklore remedies attributed to the cotton plant to determine if gossypol is in reality the active agent.

Gossypol and its derivatives have been shown to have significant antimicrobial activity as well as wound healing effects and may find application in ointments (42–44). It also exhibits antimalarial activity and is reported to kill viruses such as herpes (45–47). Gossypol samples distributed by SRRC have been instrumental in the discovery that it is a very powerful inhibitor of Chagas disease, a deadly Central and South American parasitic disease that is this continent's equivalent of African sleeping sickness and for which there was no effective treatment (48–50). Gossypol has also been found to have inhibitory activity against human pancreatic carcinomas, and was reported to kill 90% of melanoma and colon carcinoma cells and may be of potential therapeutic value in this area (51–53). Additionally, gossypol inhibits the conversion of pepsinogen to pepsin, which in non-

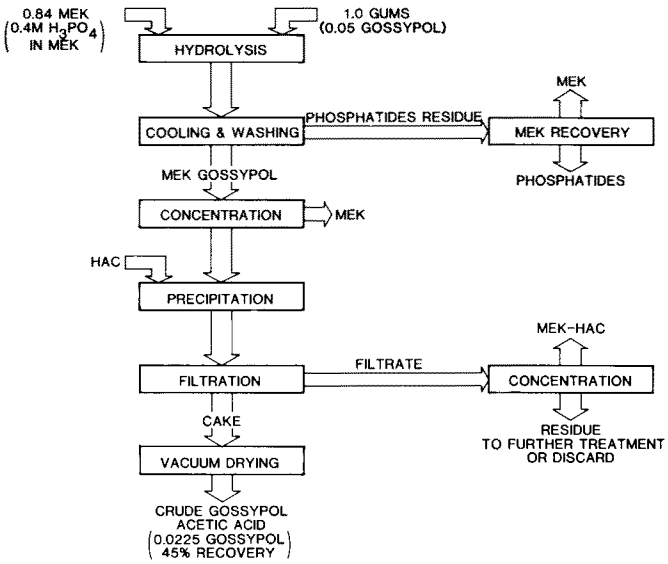


FIG. 4. Flow sheet for the recovery of gossypol acetic acid from gums.

ruminant animals would affect the digestion of cottonseed products (54,55). Its use as an appetite suppressant has been reported on numerous occasions over the last 50 years; serious interest in it developed in 1947 (56), until further investigation of its possible toxic effects at low level doses resulted in the death of several experimental dogs (57). The toxic effects of gossypol on man have largely been assumed because of its effects on animals, even though each animal's reaction can vary significantly (58). Swine, guinea pigs and rabbits are the most sensitive, cats and dogs have intermediate sensitivity, and poultry, mice and rats have low sensitivity. Ruminant animals, except for young calves, generally are not affected by the levels of cottonseed commonly used in feeds. There are no recorded instances of deaths in humans directly attributed to gossypol-containing products (59).

This leads us into the accidental discovery of gossypol as a male contraceptive. In 1957 a Chinese researcher

named Liu reported in a Shanghai medical journal that Wang village in Jiangsu, China had not had a single childbirth for roughly 10 years between the 1930's and 40's. Before and after this period there did not seem to be a birthing problem. Liu found that, due to poor economic times, the people of this village switched to using crude cottonseed oil in their cooking. Liu suggested that the gossypol contained in the oil might be the cause of female infertility (60). His findings were ignored until 1967, when medical workers in six provinces reported observance of a disease called "Burning Fever," caused by the ingestion of crude cottonseed oil, one of whose symptoms was infertility. They put the three findings together in 1972, demonstrated the antifertility effects of gossypol on rats and monkeys (61-64) and initiated the first clinical trials in man (65). This opened the door to numerous researchers, who have since shown gossypol to be an effective and reasonably safe male antifertility agent when tested at an initial 20 mg per day oral dosage level for 3 mo, followed by 50-60 mg weekly maintenance dosage levels, on over 9,000 men for as long as four years (66). The initial dose reduces sperm motility and subsequent maintenance doses additionally, and more importantly, block sperm production. A potassium deficiency side effect was directly attributed to diet (65) and there were some reports of a small percentage of men, mostly over 35, who failed to regain their fertility (67). Research is continuing on the contraceptive effect of gossypol.

Although the gossypol obtained from the cotton plant via the acetic acid complex is optically inactive, gossypol obtained from the leaves and flowers of the tropical tree *Thespesia* is strongly positive (4,68). Recently, investigators have used HPLC methods to separate small quantities of racemic gossypol from the cotton plant into its (+) and (−) isomers (69,70). But a possibly overlooked large source of (+) gossypol from the cotton plant may be easily obtainable from mother liquor resulting from the precipitation of the gossypol-acetic acid complex from gossypol-containing solutions (20). Approximately equal quantities of (+) gossypol, which will not precipitate with acetic acid, may be available in this mother liquor. This would also explain the low, 45% recovery of gossypol acetic acid reported for this reaction. Although both isomers and the (+−) racemic form kill sperm cells in vitro, the negative isomer and racemic form when taken orally are the only forms which show antifertility activity (41,71-74). The positive isomer, although non-toxic, is inactive orally in males but may find application as a female contraceptive when used as an aborting agent or as a topical vaginal spermicide (75). Further research with the optical isomers may result in more significant discoveries.

Gossypol is presently a very valuable commodity to at least one group, the chemical supplier, but as a valuable byproduct of the cottonseed industry its time has not yet come. However, because of its potential as a male contraceptive, many scientists are evaluating it using new instrumental techniques that may still indicate a valuable use. Since the four to five million metric tons of cottonseed produced annually in the United States contain up to 27 million kg of gossypol, a well defined use could equate to a very valuable market for this much maligned product of the cotton plant.

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