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Review

Extracts of Peanut Skins as a Source of Bioactive Compounds: Methodology and Applications

Lisa L. Dean

Food Science and Market Quality and Handling Research Unit, USDA, ARS, SEA, Raleigh, NC 27695-7624, USA; Lisa.Dean@usda.gov; Tel.: +1-919-515-9110

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Featured Application: Optimized extraction of polyphenols from peanut skins.

Abstract: Peanut skins are a waste product of the peanut processing industry with little commercial value. They are also significant sources of the polyphenolic compounds that are noted for their bioactivity. The extraction procedures for these compounds range from simple single solvent extracts to sophisticated separation schemes to isolate and identify the large range of compounds present. To take advantage of the bioactivities attributed to the polyphenols present, a range of products both edible and nonedible containing peanut skin extracts have been developed. This review presents the range of studies to date that are dedicated to extracting these compounds from peanut skins and their various applications.

Keywords: peanut skins; peanut testa; peanut processing; polyphenols; procyanidins; agricultural waste; bioactivity; antioxidants

1. Introduction

The global production of peanuts is projected to be 47 metric tons for the 2020 crop year [1]. In addition to the edible kernel, the peanut seed consists of the woody outer shell and a paper-like substance that surrounds the kernel itself known as the testa or skin. For most peanut products, the skin is removed and discarded [2]. The skin removal is done by a process known as blanching, which subjects the shelled raw peanut kernels to mild dry heat treatment and mechanical abrasion. The skin portion represents approximately 3% of the total kernel mass, resulting in thousands of tons of this material being produced each year which has no real food value. It has some applications in animal feed but is limited by the bitter flavor and high levels of protein binding components, which have been identified as polyphenols [3–5]. It is these polyphenolic compounds that have proven to give value to peanut skins. Information on peanut skins has briefly been included in a recent review [6]. Readers are referred to another recent review for a more complete discussion of the types of phenolic compounds that are found in nuts, including peanuts [7]. This article reviews the bioactive compounds present in peanut skins with an emphasis on the extraction methodology that has been developed to recover them.

2. Extraction of Peanut Skins

2.1. Compound Identification

The first reported attempts to chemically characterize peanut skins were concerned with their pigmentation. Off colors in isolated peanut protein were attributed to high molecular weight polyphenols or tannins leaching from the peanut skins during processing [8]. An early review of the protein-bound anthocyanins identified peanut skins as a source of those compounds [9]. Tannins were

known for their metal-chelating properties and peanut skins were reported as an inexpensive source of these compounds that could be complexed and used to remove heavy metals from wastewater [10]. Removal of skins was also proposed as a method to reduce the aflatoxin content of peanuts [11]. This fungitoxicity led to research on the relationship of the content of these compounds with peanut maturity [12]. One of the first studies to try to elucidate the actual structure of the compounds investigated the possibility that peanut skin extracts might be a substitute for pine bark in preparing phenolic resins [13].

The early reports of extraction of peanut skins were concerned with removing compounds that caused discoloration of the kernels and were not concerned with protecting or recovering these compounds for further use [14]. In some cases, the solvents used are listed but the mixtures are not adequately described to determine how they have been used [15]. Extractions for identification of these compounds followed schemes that utilized the affinity of the hydroxyl groups present for polar solvents mixed with water [13]. Considering the compounds of interest would be similar to those of peanut hulls, methanol alone was used to prepare extracts of peanut skins that were tested as antioxidants for sunflower oil without determination of the identity of the compounds [16]. The findings that peanut skin extracts had antioxidant activity in a vegetable oil model led to studies to optimize the total phenolic content recovered using different solvent systems [17]. Table 1 lists the results from the solvent trials.

Table 1. Extraction percentages (wt %) of antioxidant components and phenolic total contents (mg/g) of the extracts from peanut skins using different solvents [17].

Extract [a]	Extraction Percentage [b]	Phenolic Total Content [b]
ME	17.9 (cd) ± 0.6	148.7 (d) ± 3.6
EE	18.5 (cd) ± 0.2	114.8 (c) ± 5.9
KE	19.4 (de) ± 0.6	61.4 (a) ± 1.4
AE	9.9 (a) ± 0.1	58.5 (a) ± 2.4
dME	17.1 (cd) ± 0.9	165.6 (a) ± 16.2
dEE	16.2 (c) ± 1.1	150.4 (d) ± 9.1
dKE	13.1 (b) ± 0.1	65.5 (a) ± 1.8
dAE	10.0 (a) ± 0.3	90.7 (b) ± 1.1

[a] Abbreviations: ME = Methanolic extract, EE = Ethanolic extract, KE = Acetonic extract, AE = Aqueous extract. The addition of the letter "d" signifies defatted peanut skins. [b] Means followed by the same letter within each column are not significantly different at $\alpha = 0.05$.

Using a series of extractions, better isolation was possible for the identification of the actual compounds present in peanut skins [18]. Beginning with hot water, the bulk of the polar compounds was removed. The solution was passed through a non-polar polymer resin (HP20), and the hydroxylated compounds were then eluted with aqueous acetone (70%). The residue remaining after solvent removal was further purified by extraction with ethanol (95%). After solvent removal, the resulting residue was passed through a size-exclusion resin. Different fractions (12) were eluted from the resin using several combinations of aqueous acetone with and without the addition of acetone. With several purifications using silica gel, followed by a final separation using preparative High-Pressure Liquid Chromatography (HPLC), several fractions were produced that were finally recovered using recrystallization to allow for identification using Nuclear Magnetic Resonance Spectroscopy (NMR).

Peanut skins have been used in traditional Chinese medicine preparations to treat conditions such as chronic hemorrhages and bronchitis. To investigate these applications, the compounds extracted using aqueous solvent mixtures were identified as the A-type proanthocyanidins [18]. Some of the phenolic containing compounds isolated in this study were found to inhibit the activity of hyaluronidase, an enzyme which has been found to increase in the presence of certain cancers [19]. A follow-up study further isolated and purified the extracts [20]. From the NMR spectra, the alkaloids, 3-methoxy-3(3-indolyl)-propionic acid, 2-hydroxy-3-[3-(1-N-methyl)-indolyl]-propionic acid, and 2-methoxy-3-(3-indolyl)-propionic acid were identified. The authors reported that the first

two compounds had never been isolated from a natural source. Other compounds identified were several flavonoid glycosides. Further research with this extraction technology allowed for the isolation and identification of several oligomeric proanthocyanidins [21]. The activity of the flavan-3-ols, catechin and epicatechin and their oligomers, and the proanthocyanidins has been the subject of research in cocoa sources and tea [22]. As those found in peanut skins are composed of the A linkage form compared to the B or C forms in those other sources, comparison studied have investigated the comparative activity. The difference in the 3-dimensional structure of the compounds due to the extra 2β-O7 linkage in the A-type found in peanut skins could affect their interaction with membrane phospholipids (Figure 1).

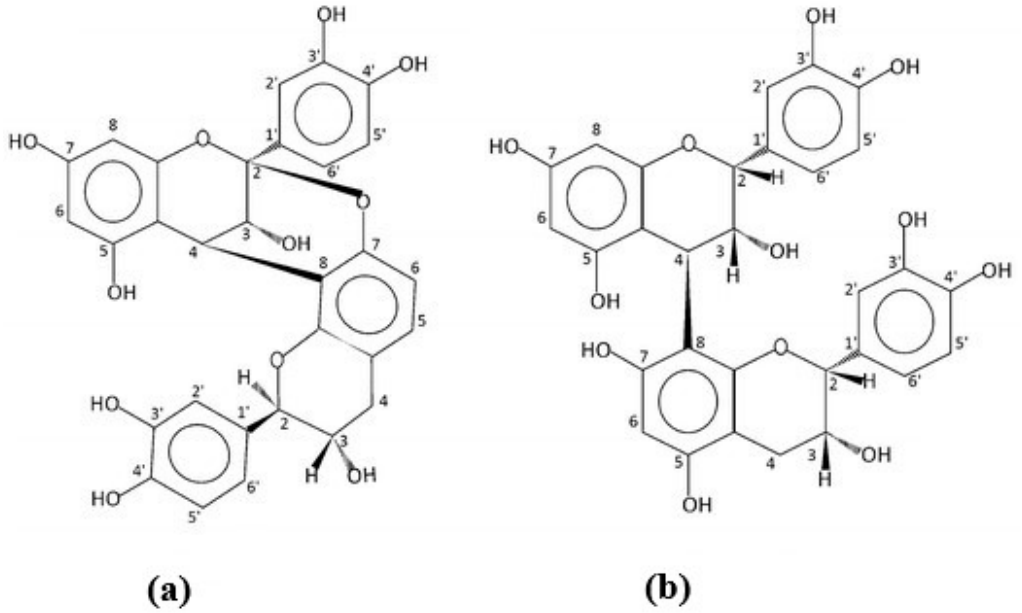

Figure 1. Structures of the procyanidin dimers. (**a**) The A-form found in peanut skins. (**b**) The B-form found in cocoa.

As this has proven to influence membrane fluidity and thus the ability of the compounds to interact with free radicals within the cell, the action of the different forms was examined [23]. A system using fluorescent probes that could be oxidized by peroxyl radicals that were induced by the assay on liposomes was used. The effectiveness was found to be dependent on the number of available flavanol monomers present, so no significant differences were seen between the types of dimers and trimers. The A-type dimer did have a different effect on the ordering of the core, with different rigidification indicating a different type of reaction with this form of the dimer. It has been proposed that the rigidity of the A-type due to the additional bond between the adjoining flavan-3-ols plays a role in their interaction with large biomolecules [24].

The color of peanut skins has been proven to have a relationship with the composition of the phenolic compound present [25–29]. In an examination of all the market types with skin colors from light brown to dark red, total flavonoids were not found to be as closely correlated to skin color as they were to growing location. The statistical relationship between the total flavonoids and the procyanidin content indicated that these compounds are the major flavonoids present. This indicates these compounds are more sensitive to stress conditions. The total phenols were more closely related to the hue of the skin color. Only the peanuts with the black seed coats were found to contain cyanidin-3-O-sambubioside both free and in glucosides [27]. Black seed coated peanuts were used to study the genetic control of peanut seed coat color [30]. In this report, the flavonoids present in white, red, and striped peanut skins in addition to those in the black peanut seed coats were extracted using 75% methanol in water acidified with 0.5% acetic acid.

The extracts were filtered, and the flavonoids were identified and quantified using High-Pressure Liquid Chromatography-Mass Spectrometry-Time of Flight (HPLC-MS-TOF). Although different flavonoids and their glycosides were found to be unique to the different colored peanut skins, they were found to have the same biosynthetic pathways for anthocyanins but with different modifications. Individual flavonoids were isolated and identified from the skins of black seed-coated peanuts after extraction with acidified water followed by a partition into ethyl acetate [29]. The extracts were fractionated using Amberlite XAD-7HP resin to remove the most polar compounds followed by YMC® Gel ODS-AQHG resin to separate the hydrophilic ones and identified using High-Pressure Liquid Chromatography-Electrospray Ionization-Mass Spectrometry (HPLC-ESI-MS/MS) and NMR spectroscopy. Three unique flavonoids (quercetin-methylpentoside, quercetin-feruloyl-hexoside, quercetin-3-dihexoside) and four anthocyanins (cyanidin-3-o-sophoroside, cyanidin-3-o-sambubiside, cyandin-3-o-glucosylrutinoside, cyanidin-3-o-xylosylrutioside) were identified.

Using HPLC to determine the various compounds that compose peanut skins has advanced from initial reports of the oligomers [31]. Aqueous ethanol was the extractant for the analysis of peanut skins, and the method identified five phenolic acids (gallic acid, caffeic acid, p-coumaric acid, protocatechuic acid, ellagic acid), two stilbenes (piceid, resveratrol), and eight flavonoids (catechin, epicatechin, epigallocatechin, catechin gallate, epicatechin gallate, epigallocatechin gallate, procyanidin B_2, quercetin). This report validated the methodology for the quantitation using the runner, Spanish, and Virginia market types. Concentrating specifically on peanut skins from the Virginia market type, a study compared the compounds extracted when either methanol, ethanol, acetone, or water at boiling temperature was used individually [32]. Using 100% acetone resulted in the highest amount of the smallest phenolic compounds. The study used HPLC-MS^n to identify a range of compounds that were polymers of catechin and epicatechin with and without sugar moieties up to 9 catechins. These polymers were found mostly in the A form. An advanced study to determine the content and structural formation of the trimer and tetramer of the procyanidins used extraction with 30% methanol in water followed by 70% acetone in water [24]. The extracts were combined, and the solvent was evaporated to dryness. The dried material was dissolved in water and partitioned against ethyl acetate containing increasing amounts of aqueous ethanol (5%, 10%, 15%). The extracts were then loaded onto silica gel and rinsed with a series of solvents to purify and isolate the components. Identification was performed using NMR and electron circular dichroism spectroscopy (CD). The different polymers were tested for anti-inflammatory activity in a macrophage system and the tetramers were found to be the most effective with the dimers having little or no effect. This showed that biological systems could differentiate between the different forms of the procyanidins.

As studies became more sophisticated to examine the composition of peanut skins in order to determine the source of bioactivity, multistep extraction schemes were used to selectively isolate certain compounds. A series of methanol and water mixtures was used to remove specifically the A-type procyanidins [33]. Drawing on previous research, the extraction scheme was created [18,20,21]. Peanut skins were extracted sequentially with 20% aqueous methanol, 70% aqueous methanol, and then finally 70% aqueous acetone. Each fraction was concentrated and then partitioned into ethyl acetate to remove soluble saccharides. The fractions were then analyzed by HPLC-MS, which revealed the 20% methanol fraction contained mostly oligomers of the A-type procyanidins and the 70% acetone fraction contained larger polymers. The use of peanut skins as a specific source of compounds for isolation has been described. Peanut skin has been a source of resveratrol and was extracted using 20% ethanol in water [34]. Increasingly, previously unidentified compounds have been reported from peanut skin extractions. Researchers have described an A-type procyanidin (epicatechin-(2β→O→7,4β→8)-[catechin-(6→4β)]-epicatechin) that had not been reported before after extraction of peanut skins with 70% acetone in water, followed by fractionation on Sephadex LH-20 and elution with ethanol [35].

Research to differentiate between the classes of procyanidins present in peanut skins has used the technique of hydrogen/deuterium exchange (HDX) to elucidate the structural differences between

isomers [36]. The technique was able to differentiate between the A-type procyanidins in peanut skin extracts containing up to three linkages. The extracts were prepared using 70% acetone in water containing 0.1% formic acid after defatting of the peanut skins. The filtered extracts were dried under nitrogen gas and then reconstituted in the deuterated mobile phase.

As a follow-up to a previous study of the composition of whole peanuts, the authors used the same extraction system of 80% methanol in water after defatting with hexane to compare peanut skins from two different peanut market types [37,38]. The analysis using HPLC-MS of the extracts found that the Valencia market type peanut skin extracts had higher levels of flavonols, quercetin, and its methylated analog, isorhamnetin.

One of the most complete studies of the phenolic type compounds in peanut skins used the extraction procedure developed for the analysis of grains to prepare samples for instrumental analysis [39]. The peanut skins analyzed were obtained after commercial blanching, which requires mild heat treatment. As heat treatment has been reported to liberate smaller phenolic compounds from larger polymers, this proved advantageous in allowing for a range of identifications [40]. Acidified water was used for the initial extraction followed by a partition into diethyl ether to capture the free phenolic compounds. A solvent exchange of methanol for the ether was performed before the analysis by HPLC-MS. From this, 88 individual phenolic type compounds were found, although some could only be identified by their class (Table 2). In addition, 60 proanthocyanidins were found, with most being of the A-type. The same group used the same extraction scheme with fractionation to determine the bound phenolics [41]. After the extraction and portioning of the free phenolics into diethyl ether, the aqueous phase was then base-hydrolyzed and acid-hydrolyzed to convert the ester derivatives to their carboxylic acid or flavonoid analogs. The analysis was then done with the same LC-MS system. An additional 78 compounds that existed as esters or glycosides were tentatively identified. The reader is referred to these publications for the listings of these compounds.

Table 2. Content of selected phenolics quantified in dry-blanched peanut skins (PS) by C18 Reverse Phase High-Pressure Liquid Chromatography (RP-HPLC) [39].

Free Phenolic Compounds [a]	Content [b] (mg/100 g)
Protocatechuic acid	3.43 ± 0.04
p-Hydroxybenzoic acid	1.03 ± 0.06
Caftaric acid	51 ± 0.12
cis-Coutaric acid	10.1 ± 0.52
trans-Coutaric acid	2.11 ± 0.08
p-Coumaroyl-O-pentoside	5.52 ± 0.23
p-Coumaric acid	0.53 ± 0.06
Chicoric acid	3.44 ± 0.12
p-Coumaroylcaffeoyltartaric acid	2.26 ± 0.13
Chicoric acid	3.12 ± 0.13
di-p-Coumaroyltartaric acid	13.8 ± 1.53
p-Coumaroylsinapoyltartaric acid	6.32 ± 0.94
p-Coumaroylferuloyltartaric acid	5.87 ± 0.71
trans-Resveratrol	0.36 ± 0.05
Quercetin	2.11 ± 0.27
Isorhamnetin	1.51 ± 0.02
Diosmetin	0.40 ± 0.01

[a] Caftaric acid and chicoric acids were quantified as caffeic acid equivalents; coutaric acids and other p-coumaroyl derivatives were quantified using p-coumaric acid equivalents; isorhamnetin and diosmetin were quantified using corresponding flavonoid aglycone equivalents. [b] Values are reported as means of triplicate analyses ± standard deviation. Findings are reported as mg respective phenolic/100-g dry weight (d.w.) of dry-blanched PS.

2.2. Extraction Optimization

The microwave-assisted extraction was another method used for peanut skins [42]. In this case, 30% ethanol in water was chosen as this had previously been proven to be the optimum for total phenolic extraction [43]. Surface response methodology was used to determine the power and time to extract the highest total phenols without decreasing the antioxidant effect. It was reported that 30 s at 90% microwave power produces the optimum product.

As the interest in recovering phenolic compounds from peanut skins increased, studies to optimize their recovery were done. Most of these studies concentrated on achieving the highest values using the Folin-Coicalteu assay rather than any defined class of polyphenols [44]. Factors such as particle size of the skin material, the proportion of solvent to the mass of skins, contact time with the skin material, maceration or shaking, and the number of extractions using 70% ethanol in water were evaluated. The efficiency of the extraction was evaluated using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay for free radical scavenging power, which indicated that the method of agitation was not significant and that 10 minutes of extraction at 40 mL per 5 grams of peanut skins using 4 extractions was optimum. An optimization study examining proanthocyanidins from peanut skins used aqueous ethanol and ultrasonic extraction [45] (an aqueous solution of ethanol (55%) at an outlet power of 120 W at 35 °C). This resulted in the extraction of proanthocyanidins with a yield of 12.1%.

Water only was used to extract primarily the procyanidins that were then used to evaluate the potency to suppress allergenic response [46]. Further purification of the extracts was done with a reverse-phase resin to bind the polyphenols. Successive elutions were made with increasing concentrations of acetone in water and finally with 80% ethanol in water. The final eluate was then further purified using a size-exclusion resin, followed by a gel filtration resin and finally with silica gel to isolate specifically the procyanidin A-1 for further testing. When compared with the unpurified extract from the peanut skins, the isolated compounds were not as potent in suppressing immunoglobulin synthesis and regulating systemic T helper cytokine production.

Studies dedicated to the optimization of the extraction of phenolic compounds from peanut skins used response surface methodology and various chemical assays for comparisons [47,48]. Ethanol and methanol at concentrations of 30%, 60%, and 90% in water were compared with pure water and pure ethyl acetate. The total phenolics recovered (TPC) were optimized in ethanol at 30% (118 mg Gallic Equivalents per gram skins) and in methanol at 60% (112 mg Gallic Equivalents per gram skins). Pure water recovery was lower at 81 mg and ethyl acetate recovery was an order of magnitude lower. Using the Oxygen Radical Absorbance Capacity (ORAC) activity as the measure of antioxidant activity, the optimized alcohol extracts were similar (2050 μmol Trolox equivalents per gram for ethanol and 2149 μmol Trolox equivalents per gram for methanol). Pure water was less than half as effective. Varying the temperature of the extraction was investigated in this study. Increasing the temperature from 30 °C to 60 °C using 30% ethanol in the water had no effect on the TPC recovery but when using 30% methanol, increasing the temperature to 60 °C resulted in a 20% increase in the TPC. This was attributed to methanol being better able to solubilize more polar compounds. The use of microwave-assisted extraction was compared with the solvent extractions using conventional heating and mechanical shaking with the optimized solvent mixtures. The microwave procedure increased the ORAC activity to 2789 μmol Trolox equivalents per gram when using the 30% ethanol in water mixture as the extraction solvent. The main savings in this procedure is the time involved was less without compromising the activity of the extracts. Optimization of extraction using responsive surface methodology was also used to find the most effective conditions to extend oil shelf life [48]. Using ethanol in water over a range of 20% to 100% with a variation of time from 5 to 150 min and temperature from 25° to 90 °C, the study used both the DPPH and the 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS+) assays to determine the optimal conditions. It was found that length of time was not of significance but that temperatures above 60 °C with 75% ethanol in water were optimum. In addition, soybean oil with the optimized extract added at 25 to 1000 mg/kg was subjected to accelerated conditions of agitation at 60 °C and compared to the addition of 200 mg/kg of butylated hydroxytoluene (BHT), a synthetic

antioxidant compound. It required 750 mg/kg of the optimal extract to produce the same antioxidant effect of 200 mg/kg of BHT, the synthetic chemical antioxidant.

Isolation of specific proanthocyanidins was performed using preparative HPLC [49]. This allowed for more automated separation of peanut skin extracts. Using earlier work as a guide [21,32], acetone in water (60%) that had been acidified was used as the extractant. An initial purification was performed using Amberlite resin eluted with methanol. This was followed by fractionation on Sephadex LH-20. The fractions were evaluated using the DPPH assay and the most active fraction was further purified using preparative HPLC. This allowed for the isolation of proanthocyanidins A1 and A2 with the major portion of the isolate being the A1 form. The most recent study of the composition of peanut skin extracts compared them to grape skin extracts [50]. The skins were extracted using 80% ethanol in water following a procedure previously published [44]. The extracts were purified using AB-8 resin to purify the procyanidins. The extracts were then evaluated using ORAC, DPPH, ABTS+, and the Ferric Reducing Antioxidant Power (FRAP) assays as well as a cell assay using Human hepatocellular carcinoma (HepG2 cells). Both the A- and the B-type of the procyanidins were identified by HPLC-MS with the A-type predominating as found by others. In most of the assays, the peanut skin extracts had slightly higher values than the grape skin extracts, with the exception of the cell-based assay where the grape skin extracts scored higher. To release the phenolics from peanut skins by the degradation of the actual cell walls for the skins, enzymatic digestion was used [51]. Cellulase was used at an incubation temperature of 55 °C followed by extraction with aqueous ethanol at 45%. The yield of proanthocyanidins was 16.17%.

An exploration of the effectiveness of heat in increasing the solubility and thus the extraction efficiency of solvent in removing phenolic compounds from peanut skins was performed. As many of these compounds are found to be bound into sugars and other cellular structures, the authors theorized that heat treatment of the skins before extraction would increase the yield [52]. Using temperatures from 90 °C to 180 °C, peanut skins from the market types, runner, Virginia, and Spanish were extracted using 70% ethanol in water solutions. TPC and antioxidant activity using the Trolox equivalent antioxidant capacity (TEAC) and the Peroxy-radical trapping capacity assays were compared. Heating to 135 °C resulted in the highest TPC in the runner peanuts (280 mg/g). Both the Virginia and Spanish peanuts did not show any significant change in TPC with heating within the tested range and were both lower (149 mg/g for the Virginia type and 137 mg/g for the Spanish type) than the runner type. Correspondingly, the activity of the peanut skin extracts was not significantly different between the market types (1.38 mg TEAC/g dry skin), except for the higher value of the runner type peanuts heated at 135 °C (2.56 mg TEAC/g dry skin). Only the runner type peanut skins showed any significant Peroxy-radical trapping capacity. The increase in TPC in the runner type was attributed to the formation of Maillard products due to the heat treatment and/or the liberation of phenolics from larger complexes. The differences in market types were attributed to different types of phenolic compounds or complexes being present and some may have been more labile to heat.

2.3. "Green" Extractions

Supercritical extraction uses pressure to condense a solvent or solvent mixture with temperatures above the boiling point of the solvents so that the dielectric constant is decreased [53]. This results in a change in the polarity so that it becomes similar to solvents such as methanol, ethanol, and acetone at room temperature. This allows for the use of more "green" or less toxic chemicals to be used with enhanced solubility of phenolic compounds in the case of peanut skins. A study using this technology optimized the total phenolic content of extracts from peanut skins to be 10 min at 220 °C using 60.5% ethanol in water [53]. This shows the potential of using a more environmentally friendly technique. Further study with this technique to extract peanut skins determined the effect of the size of the particles of peanut skin extracted [54]. Peanut skins milled to particle sizes of 300, 355, 425, and 500 μM were extracted using both traditional Soxhlet extraction and supercritical extraction using carbon dioxide. Optimum yields per weight were obtained by both methods when the particle size was

425 μM and pure ethanol was the solvent compared to either pure water or n-hexane. Although the yield from the Soxhlet extraction using ethanol was higher (36.38% by weight) than carbon dioxide using the supercritical system (15.53%), the antioxidant activity using the DPPH assay was higher for the supercritical system (93.43%) than for the Soxhlet extraction (62.11%). This was attributed to less temperature degradation of the polyphenols by the lower temperatures of operation for the supercritical system. The catechin recovery from this system was higher (139.92 μg/g peanut skin) compared to Soxhlet extraction (31.79 μg/g peanut skin) when ethanol was used as the solvent [55]. More recently, this system has been used to prepare extracts for investigations into the antioxidant protection in cell systems [56]. The extracts were compared to the activity of quercetin, which was thought to be the main compound present. After proving the additives were not cytotoxic up to 250 μg/mL, O_2^- scavenging activity was assayed. Quercetin was assayed to be seven times higher than the peanut skin extract, which was attributed to the pro-oxidant properties of the catechins present in those extracts. The addition of the quercetin and the peanut skins along with an oxidative stressor was proven to be protective against oxidative stress, whereas pretreatment was not.

A system that used ultrasound was applied to peanut skins with the specific goal of recovering the stilbenoid, resveratrol was reported [57]. *Yeast* CICC1912, *Aspergillus oryzae* 3.951, and *Aspergillus niger* 3.3148 were immobilized onto cellulose beads. Peanut skins were extracted with 80% ethanol in water and the extract was dried. Optimization of the recovery of resveratrol was performed using several surfactants, liquid-solid ratios, ultrasonic powers, and culture temperatures and times. At the optimized conditions, recovery of 96.58 μg/g of resveratrol was obtained, which was four-fold higher than from an untreated sample.

3. Bioactive Compounds in Peanut Skins

3.1. Chemical Antioxidant Activity

The antioxidant activity of peanut skin extracts was first investigated as a side project from research on peanut hulls [16]. The total phenolic content was reported using the Folin-Coicalteu assay and the antioxidant activity in sunflower oil was reported to be less than that of BHT, a commonly used synthetic antioxidant ingredient for food oils. Isolated compounds from peanut skins using a series of extractions and chromatography were found to have free radical scavenging ability when evaluated using the DPPH assay. These included flavonoid glycosides [19] and proanthocyanidins [21].

A comparison study of several black seed-coated peanuts with red seeded ones evaluated the total phenolic content (TPC), content of several phenolic classes of compounds, and several antioxidant assays [28]. Extraction of the peanut skins was performed using 70% acetone in water acidified with acetic acid after defatting with hexane. The TPC was not found to vary widely between the varieties. The skins from red seed-coated peanuts were found to be higher in total flavonoid and total condensed tannin content than the black seed coated ones, although the black peanut skins had higher anthocyanin contents. Correspondingly, one of the red seed-coated peanut types had higher antioxidant power when measured using the FRAP assay but all the peanut skins from the seeds tested had similar free radical reducing power when measuring using the DPPH assay.

Phenolic compounds in peanut skins are increased by stress conditions. Fungal attack as a source of stress was investigated [58]. Peanuts with skins of red, reddish-brown, and black colors were inoculated by the fungus, *Rhizopus oligosporus.* The seeds were then germinated for 3 days in the dark. The germinated seeds and ungerminated seeds used as the controls were extracted using a mixture of acetone, ethanol, and water (2:2:1 v/v/v) that had been acidified. From the extracts, 45 different compounds including phytoalexins were identified using HPLC-MS. In addition, the antioxidant activity was determined using total phenolic content (TPC), total flavonoid content (TFC), oxygen radical absorbance capacity (ORAC), hydroxy radical absorbance capacity (HORAC), superoxide radical absorbance capacity (SORAC), and DPPH. In general, the black skins had higher activity in most of the

assays, with the exception of SORAC. The red and reddish-brown colored skins tended to be similar in strength. In most cases, the treated seeds had higher activity than the untreated controls.

Aqueous methanol continued to be used in studies after defatting with hexane [59]. The extracts were found to have little antioxidant activity when incorporated into vegetable oils and lard but were found to test high in free radical activity testing using chemical tests. The extracts were found to have metal-chelating activity. The same extraction scheme was used to compare the effectiveness of skins from high oleic peanuts with those from peanuts with normal oleic acid levels [60]. No significant differences were found in the antioxidant power of the extracts from the two different types of peanuts.

The use of several solvents individually without the addition of water was studied to determine the yield of soluble material by weight [61]. The highest recoveries were from ethanol, followed by methanol and acetone. Although the amount of solids recovered from these solvents was equivalent (ca. 200 mg from 5 g peanut skin), the acetone extract had only 3% of the antioxidant activity compared to the alcohol extracts (3% vs. 9.8% for ethanol and 93.5% for methanol) using a β-carotene-based assay. Hexane and ethyl acetate yielded much less solid material (35 mg and 90 mg, respectively) and comparable activity to the acetone extract (3%). This proved the active components are polar compounds. Differences between peanut skin extracts from raw and roasted peanuts were determined using a series of solvents and solvent mixtures [62]. Pure ethanol, 80% ethanol in water, pure ethyl acetate, and 80% ethyl acetate in water were used. The highest yields by both weight and total phenolic compounds were found with the ethanol in the water mixture followed by pure ethanol. Higher levels were also found in the roasted peanut skins compared to the peanut skin extracts from the raw peanuts. The roasted peanut skin extract prepared using 80% ethanol in water was found to be effective as an antioxidant when added to sunflower oil, but even at 800 ppm, the effectiveness as monitoring using the Peroxide Value assay was less than that of BHT added at 200 ppm. Using only methanol, raw peanut skins were extracted for determination of total phenolic content (TPC), antioxidant activity using the DPPH assay, and inhibition of linoleic acid peroxidation [63]. Only 91.74 mg/g of TPC were found in this study compared to 148.7 mg/g reported in another study [17]. This is an example of the variability of the levels of extractable compound present in peanut skins.

The effectiveness of different solvent mixtures in terms of antioxidant activity was compared with ethanol and methanol [40,64]. Methanol or ethanol in water (80%) were used. The lipid in the extract was removed by partitioning into chloroform. The aqueous portion was then extracted with ethyl acetate to remove the nonphenolic compounds remaining as described by the methodology developed for purifying phenolic compounds from tea [65]. The aqueous portion was freeze-dried and the resulting powder dissolved in methanol for testing. A combination of solvents was used to prepare extracts from different parts of the peanut, including the skins that contained the different classes of polyphenols [66]. The initial extraction of peanut skins from a local market was performed using equal parts of methanol and water. The skins were then extracted with 70% acetone in water and the 2 extracts were combined. This represented the extractable polyphenols in the authors' description and was used to determine the total phenolic content (TPC) using the Folin-Coicalteu assay. The non-hydrolyzable polyphenols or condensed tannins were determined after treating the extracts with acidified butanol. The extracts were then evaluated using chemical assays for antioxidant activity, anticancer activity in a cell-based assay, and as an antioxidant by the heating of oil spiked with the peanut skin extracts.

The solvent mixtures and solvent-assisted extraction were used in a study of various portions of peanuts including peanut skins [67]. A mixture of acetone and water (70%/30%) was acidified and used as the solvent. Acidification was used to free phenolics from glycoside complexes. Peanuts were subjected to increasing time of roasting to produce Maillard browning products. Increased roasting was found to increase the total phenolic content as well as corresponding ORAC assay values. A methanol/water mixture (50/50 v/v) followed by a mixture of acetone and water (70/30 v/v) was used to extract peanut skins, hulls, and defatted peanut flour, both raw and roasted [66]. The extracts were evaluated using TPC, nonhydrolyzable tannins (NEPP), and oxidative stability test on flaxseed

oil. The extracts from the skin tested much higher than the other parts of the peanut with the roasted samples being lower than the raw ones.

The procyanidins have been found in a range of plant parts in several forms. Comparison of those found in peanut skins with those from other foods has been the subject of several studies [7,23,65,68,69]. As previously discussed, peanut skins contain primarily the A-type. One report revealed both A-type and B-type dimers showed high antioxidant potency in a dose-dependent manner in the DPPH and ABTS+ assays [70]. However, the type of system used had an effect. In general, the B-type dimers showed a higher radical scavenging potency when tested in aqueous systems, whereas in tissue or lipid systems, the A-type dimers were just as effective or had even higher antioxidant potency than B-type ones.

Comparisons of the activities of extracts from peanut skins with other agricultural by-products used extracts prepared using 80% ethanol in water [71]. Of the materials tested, mango and grape skins and seeds and peanut skins, the highest amounts of flavonoids and total phenolics were found in the peanut skins on a dry weight basis. The DPPH activity of the peanut skin extract (756.54 ± 65.45 mg TE/g) was not significantly different from the grape extract (728.46 ± 92.26 mg TE/g) but was higher than that of the mango extract (158.53 ± 4.95 mg TE/g). In another study, using 20% methanol in water, the types of procyanidins recovered were compared [69]. Peanut skin extracts were found to contain mainly the A-type dimers and grape skins almost exclusively the B-type dimers.

3.2. Antimicrobial Activity

As phenolic compounds are known to have antimicrobial properties, it is logical to examine the antimicrobial properties of peanut skin extracts. The first report used 80% ethanol in water to extract peanut skins [72]. The extract was used to determine the antioxidant power in meat when compared to synthetic antioxidants. While levels of 0.06% to 0.10% peanut skin extract had the equivalent power of 0.02% synthetic antioxidant in delaying the onset of rancidity in the meat samples, the inhibition of the microorganic growth was much less than a chemical antibiotic.

Certain phenolic compounds including proanthocyanidins have proven antimicrobial properties. The study of extracts from peanut skins against certain bacterial strains has used this justification [68,73,74]. Peanut skins were initially extracted into boiling water, then portioned into ethyl acetate to isolate the proanthocyanidin fraction [73]. After solvent removal, the extracts were incorporated into growth media containing apple juice to create a model food system. *Saccharomyces cerevisiae*, *Zygosaccharomyces bailii,* and *Zygosaccharomyces bisporus* were used as the test organisms in individual cultures. Although peanut skin extract proved to inhibit the yeast growth due to alteration of the cell membranes, the amount needed to be effective was thought to be too high for practical use in food. Using acetone in water acidified with acetic acid (70:28:2), hexane defatted peanut skins were extracted to recover the polyphenols [68]. Plated media were dosed with increasing amounts of the extracts in water from 250 to 1500 ppm. The plates were inoculated using *Salmonella typhimurium, E. coli* OH157:H7, or *Listeria monocytogenes* as the test organisms. No inhibition of *Listeria monocytogenes* was seen by the addition of peanut skin extract and less inhibition was seen in the growth of the other organisms tested when compared to similar amounts of grape seed extracts. This was attributed to the B-type procyanidins present in grape seed extracts being more effective than the A-type procyanidins found in peanut skin extracts. Comparison of the antimicrobial effects of extracts from peanut skins with those from dry blanched peanuts used 70% acetone in water as the extractant [74]. The peanut skin extracts were found to be less effective in inhibiting the growth of a range of both gram-positive and gram-negative organisms by an order of magnitude. This was attributed to the phenolics from the blanched peanut extracts containing small phenolics rather than polymers of phenolic compounds. Peanut skins were extracted with 80% ethanol in water and then either freeze-dried or spray-dried with maltodextrin as a carrier [74]. The antimicrobial action against *Staphylococcus aureus*, *Listeria monocytogenes*, *Salmonella enterica* subs. *Enterica* serovar Enteritidis, and *Escherichia coli* was evaluated. None of the powders showed any inhibition of

Escherichia coli. The freeze-dried extract was the most effective in inhibiting the other pathogenic organisms. Although the spray-dried extracts were inhibitory as well, the lesser degree was attributed to the dilution of the phenolic content by the addition of maltodextrin in the preparation of the powders.

Antiviral activity in peanut skin extracts has been demonstrated in cell culture trials when used in combination with antiviral drug compounds [75]. Pure ethanol was used to extract defatted peanut skins. The effect was most pronounced during the early stages of infection. The effect was attributed to the polyphenols present. The resveratrol content was also determined but not found to show concentration dependence.

Fungal growth on grain producing mycotoxins has damaging health effects when consumed and reduce the acceptability of the crops. A study demonstrates the effect of peanuts skin extracts using 70% ethanol in the water on the growth of *Fusarium verticilliodes* on maize [76]. The different fractions separated on Sephadex resin had different effects on the inhibition with only one having a large effect. The different factions were only distinguished by their visible colors. The lightest colored fraction was the most effective, which would indicate that the procyanidins were not involved.

3.3. Anticancer Activity

Being able to purify the individual polyphenol compounds, especially the procyanidins, allowed for further study of their biological effects. Using a scheme worked out earlier [21], 11 individual procyanidins of the A-type as monomers, dimers, trimers, and tetramers were identified [77]. In cultured human melanoma cells, inflammatory cytokinetic production was reduced after lipopolysaccharide challenge. Dimers and trimers showed greater effects than the monomers or tetramers. This provided scientific insight into some of the effects attributed to peanut skins by traditional medicine. The effectiveness of peanut skin extract as an anticancer agent was demonstrated using human prostate cancer DU145 cells [78]. Peanut skins were extracted using 70% ethanol in water and then subsequently fractionated by size exclusion chromatography using ToyoPearl HW-40S resin. The procyanidin B_3 was determined to be the most active against the proliferation of the cancer cells.

Resveratrol is one of the naturally occurring phytoalexins which plants produce in response to stress such as a fungal attack. Peanut skins have been reported to contain this compound [79]. This compound has been reported to have chemoprotective properties against cancer. The method of action has been proposed to be interference with the pathways of signal transduction, exert some control on cell-cycle regulating proteins, and has been shown to induce apoptosis in some cancer cells [80]. Using peanut skins as a source of these compounds, a skin-lightening effect was found using reptile cells [81].

In addition, cell systems using human tumor carcinoma cell lines (liver, colon, cervical, and breast) were treated with the extract from the roasted peanut skins. The effective dose for reducing cell survival to 50% (IC50) differed for the type of cell. The largest dose was needed for the liver tumor cells (19.3 μg/mL) and the lowest for the colon tumor cell line (10.9 μg/mL). There was no effect on the breast tumor cell line. No specific compound was identified in the study as responsible for the effects. Using the human cervical adenocarcinoma (HeLa) cell line, the effectiveness of peanut skin extracts as an inhibitor of enzymes was tested against histone deacetylase [82]. The increased activity of histone deacetylases has been associated with certain human cancers. Based on a previous publication [40], 100% methanol was used to extract peanut skins. Treatment with the peanut skin extract resulted in the accumulation of the acetylated forms of histone proteins, indicating inactivation of the deacetylases. As such, the extracts were proposed as a possible supplemental cancer treatment.

3.4. Enzyme Inhibition

The action of phenolic compounds as inhibitors of carboxylases has been reviewed [83]. This type of activity has been determined in peanut skins [84]. Acetone (70% in water) was used to extract peanut skins and the extracts were fractionated using microfiltration and Sephadex LH eluted with increasing acetone levels in water solutions. The structures of the compounds in the fraction with the

highest action against α-amylase was found to be oligomers of polyflavan-3-ols, up to 15-units in size using high-resolution Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectroscopy (MALDI-TOF-MS). These compounds were determined to contain catechin/epicatechin units together with several afzelechin/epiafzelechin units and gallocatechin/epigallocatechin units with both A-type and B-type linkages. A recent review included information about the ability of methanol extracts of peanut skins to inhibit α-amylase and lipid peroxidase [85]. Alpha-glucosidase and lipase play a role in the absorption of glucose and triacylglycerols from the diet. The inhibition of these enzymes could play a role in the management of diabetes and weight. Peanut skins were extracted using 70% acetone in water and partitioned into ethyl acetate as described in a previous study [58]. This was to ensure the extraction of the soluble phenols. The residue was treated with acid and the free phenolics were recovered in a mixture of ethyl acetate and ethyl ether [86]. Subsequent treatment at alkaline pH by the addition of sodium hydroxide freed the phenolic compounds bound into esters. A final extraction into methanol was done to recover those compounds. All the phenolic compound classes showed inhibition of the enzymes with the greatest effect being from the free phenols and the least by the insoluble bound compounds. Along with white grape pomace, peanut skins were investigated for their ability to inhibit the enzymes, α-amylase, and pancreatic lipase to propose applications for agricultural waste materials [87]. Peanut skins were extracted with ethanol using sonication, filtered, and lyophilized for analysis. Inhibition by peanut skins was found to be close to 100% for lipase and above 90% for α-amylase. These actions were higher than those of either red or white grape pomace extracts.

3.5. Effects in Animal Models

Animal models have been used to determine the effectiveness of the polyphenols in peanut skins to influence blood chemistry. Studies on rats for lowering cholesterol used the water-soluble portion incorporated into a high-fat diet [88–90]. Filtration was used to partition the extracts into a high molecular weight (MW) fraction and a low MW fraction. The findings were that the lower MW fraction was more effective in slowing the transport of cholesterol from the diet into the intestinal transport system. Further study showed that the trimer was more effective than the dimer [90]. This was attributed to the low MW fraction being better able to disrupt the micelles involved. In another study using the rat model, plasma, and liver triglyceride (TG) and cholesterol (TC) levels were significantly reduced, while fecal secretion of TG and TC was greatly increased upon peanut skin extract administration [91]. The effect of the extracts from peanut skins on the blood chemistry of the rat subjects using a water-only extraction scheme is described by an earlier publication [92]. The plasma of rats fed the peanut skin extracts as part of high fat or "Western" diet was monitored [90]. Total blood lipids were reduced by the peanut skin fortified diet. The bioavailability of procyanidin A2 was considered to be greater. Peanut skins extracted with 70% ethanol in water were used to evaluate the effectiveness of peanut skin extract to mitigate the effects of an atherogenic diet in a mouse model system [93]. The addition of 0.78% peanut skin extract to a high-fat diet produced some lowering of hepatic cholesterol and glycogen levels in the test subjects. Extracts of peanut skins prepared using 40% ethanol in water followed by elution from HP-20 resin with ethanol were used in a mouse model study [94]. The dried extract was added to the animal diet at 4, 80, and 160 mg/kg of the body weight. At the two highest dosages, reduced body weights, food intake, adipose tissue, and expression of leptin protein were reported. Extracts of peanut skins were made with either pure water or methanol to determine the protective effects of extracts against liver damage induced by chloroform (CCl_4) in mice [95]. The animal subjects were fed either 50 or 100 mg/kg of extract. One group was fed prior to injection of CCl_4 and another group was fed after injection. Ingestion of CCl_4 is known to both cause peroxidation of the liver membranes and to interfere with Ca^{2+} homeostasis, which leads to liver cell damage. By monitoring levels of certain liver enzymes in the blood of the experimental animals and examination of the liver tissues by microscopy, the study showed that the methanolic extract was better able to decrease the levels of the plasma enzymes indicating less damage than the aqueous extracts. The action of the superoxide dismutase, a protective enzyme against oxidation, was increased.

The physical examination of the liver cells also showed fewer fat cells and inflammatory damage when the methanol extracts were fed. This indicated that the antioxidant-rich methanolic extracts from peanut skins had a protective effect on the liver of the test animals. Extraction of peanut skins has become commercialized to provide material for further studies. Aqueous ethanol without further definition was described as the solvent for the extraction of peanut skins for a study of the effect of the material on the formation of blood platelets in an animal model [96]. The goal of the study was to elucidate the mechanism of the observed action on hemorrhage described by traditional Chinese medical practice.

The action of the anthocyanins from black peanut skins against UV-induced skin cell damage was reported [97]. After extraction with acidified water followed by a partition into ethyl acetate as previously described [29], the anthocyanins were isolated and used to treat human keratinocyte cells (HaCaT cells) as well as the dorsal skin of live mice. After exposure to UV-B radiation, cell apoptotic death was investigated. The effectiveness was found to be dose-responsive, but high levels were found to be toxic to the cells (over 40 μg/mL).

The abundance of tannins in peanut skins would indicate that feeding this material to animals would be advantageous in that phenolics have been reported to have anthelmintic properties, that is the ability to suppress internal parasites [98]. A study with lambs, a ruminant species, did not have positive results [99]. Animals infected with gastrointestinal nematodes did not show any decrease in fecal egg counts when fed at increasing levels up to 0.53% of their body weight per day with peanut skins incorporated into alfalfa pellets when compared to the control.

Current research in the action of components from food products has focused on the effects on the gut microbiota. Peanuts skin extracts have been investigated for this effect using a mouse model [100]. Significant changes in the organisms present in the gut were observed. Most importantly, those involved in fatty acid biosynthesis and sugar metabolism were increased. This has positive implications in the compounds extracted from peanut skins to have possible antidiabetic effects.

4. Food Applications

In food, the use of peanut skin extracts as a functional food additive has been explored in several ways. Using water alone, peanut skins were extracted to create an infusion or "tea" [101]. Since the heat was required to produce the product, the chemical antioxidant strength was evaluated using TPC, Trolox equivalent antioxidant capacity assay (TEAC), and the ORAC assay. The result showed that the antioxidant potential was preserved and increased with the amount of peanut skins treated. The infusions were also found to be higher in response to the assays than green or black tea, indicating that peanut skins could have equivalent or better health properties. The preparation of an encapsulated product from peanut skin extracts produced a free-flowing powder that could be used for incorporation into foods was reported [102]. Antioxidant properties as defined by ORAC and total TPC were described. Using the extraction scheme of 70% ethanol in water followed by partitioning into ethyl acetate, a peanut skin extract powder was produced which was then incorporated at 0.02 and 0.1% by weight into raw meat that was then processed into a salami product [103]. After drying and storage, the products were evaluated by testing to determine lipid oxidation and sensory descriptors and compared to the synthetic antioxidant, butylated hydroxyanisole (BHA). Peroxide values were lower, but free fatty acid contents were not changed over untreated control. This showed the potential of peanut skin extracts as an antioxidant from a natural source. Use of peanut skin extract as an antioxidant in fresh meat described ethanol (80% in water) extracts incorporated into chicken meat ground and made into patties [104]. After cooking, the patties were stored under refrigeration. Using the thiobarbituric acid reactive substances assay (TBARS) as a measure of lipid oxidation, the addition of the peanut skin extract resulted in TBARS scores below 1.0 mg equivalents per kg. The control samples scored close to 20, proving the effectiveness when the peanut skin extract was added at 3.00%. A similar study used 80% ethanol in water as the extractant for peanut skins and the extract produced was tested for effectiveness as an antioxidant in patties produced using ground

sheep meat [105]. Using the TBARS assay, the extract was compared to a synthetic antioxidant (BHT). The effect on the production of rancidity indicators was similar for the peanut skin extracts and BHT. Neither additive was effective against microbial growth. A brief review of the use of peanut skin extracts to preserve meat products is available [106]. This work focused on the effectiveness of peanut skin extracts, in particular the polyphenols to serve as antioxidants and antimicrobials.

Recovery of the phenolic compounds on a scale to enable the use of the extract as a functional food ingredient has been studied. The skins from black peanuts were extracted with acidified water and then adsorbed onto a variety of resins to determine the most effective one [107]. Seven different commercial resins were compared and an apolar, macro-porous styrene-divinyl benzene resin produced in China with the trade name of DM-1, was chosen as the most effective based on adsorption and ease of desorption of the proanthocyanins with a recovery of over 18% of the dry weight of the original material.

Using peanut skin extracts as an ingredient in food products causes problems due to the extreme bitterness and astringency properties of the material. These properties are attributed to the high tannin content. Using maltodextrin to encapsulate the extracts creates a free-flowing powder that is more easily handled and able to mitigate the negative flavor impacts [102]. Using the encapsulated material allowed for an increase in the chemical bioactivity as measured using the DPPH assay without changing the sensory properties when added to milk chocolate [108]. The antioxidant activity was also found to be retained and the negative sensory properties of peanut skin extract were eliminated when the encapsulated peanut skin extracts were used in flavored coatings for peanuts [109]. The bioavailability of phenolic compounds from peanut skins has been found to be low in the human intestinal tract, thus a study on producing edible films containing peanut skin extract which would allow for transfer through the oral mucosa was conducted [110]. Using a previously reported extraction scheme [44], peanut skin extract was incorporated into a gel consisting of gelatin and hydroxypropyl methyl cellulose and cast into films. Release of the polyphenols in the peanut skin extract after ingestion was found to be less than optimal due to binding with the proteins of the gelatin. Using the encapsulation procedure previously described [102], extracts of peanut skins were used to coat peanuts used in a clinical study of the hyperglycemic response [111]. Human subjects who ingested a glucose solution along with the peanut skin extracts were found to have lower peak blood glucose levels at 45 minutes. This demonstrated the antidiabetic properties of the peanut skin extract prepared in this manner. The regulation of body fat and blood glucose by peanut skin extracts was evaluated in human subjects [112]. Aqueous extracts of peanut skins were dried and enclosed in gelatin capsules for consumption. Capsules were prepared to contain 200 mg of peanut skin extract powder. Sixteen adults ingested 2 capsules twice a day for 6 weeks. Other studies have shown peanut skin extracts inhibit α-amylase [85,87], so it was hypothesized that ingestion of peanut skin extracts would influence fasting blood glucose and body fat deposition. Although none of the subjects suffered from either type 1 or type 2 diabetes, some did have abnormal fasting blood glucose levels. These individuals were the only subjects that showed a significant decline in their body fat and fasting blood glucose. None of the subjects showed any negative effects on their kidney or liver function. This shows that peanut skin extract has the potential for use in blood glucose control. A more specific study used the isolated catechin, procyanidin A_1 dimer, and epicatechin-(4$\beta\rightarrow$6)-epicatechin-(2$\beta\rightarrow$O$\rightarrow$7, 4$\beta\rightarrow$8)-catechin (EEC) trimer that had been purified from hot water extracts of peanut skins [113]. It was found that the trimer had a dose-response effect on the digestive enzymes, α-amylase and α-glucosidase, but the catechin monomer and the dimer seemed ineffective. In addition, the trimer was able to suppress glucose transport in a cell system.

As discussed above [29], extraction with acidified water followed by a partition into ethyl acetate was used to evaluate the thermal stability of the anthocyanins at pH values similar to those of various beverages such as carbonated drinks, teas, and energy drinks [114]. This was done to assess their value as functional food additives. Extracts from peanut skins using aqueous ethanol (17.7%) were used as an antioxidant in the coating for flavored peanuts and found to be as effective as BHT [115]. The effectiveness as an antioxidant in meat was evaluated using extracts prepared using only methanol

as the extractant [116]. The addition of 400 ppm of phenolics from the extract extended the shelf life of the meat by 60% without affecting the color or cooking characteristics. There was no inhibition of microbial growth, however.

5. Processing Effects

Processing effects on the activity of the bioactive compounds have been investigated. The removal of peanut skins from peanuts can involve mechanical abrasion, heat, and exposure to air. An investigation that compared hand peeling of the skins from peanuts in comparison to those from the mild heat treatment of conventional blanching and the more intense heat of roasting was compared in terms of the antioxidant properties of the peanut skin extracts [40]. Blanching was found to have a greater effect on the concentration of total phenols when compared to the roasting process. The use of ethanol was found to be a slightly more effective solvent in terms of the total phenolic content compared to methanol. To determine the processing effect on the antioxidant activity, the ABTS+ assay was used. The activity of the extracts in terms of free radical scavenging activity was found to differ with the processing effect and solvent used. For the peeled skins with no heat treatment, the activity was higher when methanol was used. For the roasted samples, the skin extract had greater activity when ethanol was used. These two systems were 10 times more effective than blanched skins regardless of the solvent used. To evaluate how peanut roasting, the most common processing procedure for peanuts, affects the bioactivity of peanut skin extracts, several procedures for removal were evaluated [117]. After peeling, blanching (light heat treatment), and roasting, the recovered skins were extracted using 80% ethanol in water solutions. Comparisons of TPC, total antioxidant activity (TAA) as free radical scavenging ability, and the DPPH assay were made. The extracts were assayed as both the crude extracts and those that had been further purified by isolating only the procyanidins. Blanching before skin removal resulted in significant losses in TPC, while roasting did not. Correspondingly, the antioxidant levels were decreased much more in the blanched over the raw peeled and roasted skins. This same pattern was reflected in the concentrations of the procyanidins recovered from the skins after process treatment. Further investigations made use of the assays already discussed to evaluate the bioactivity of peanut skin extracts but added more focused testing. The free radical and oxygen scavenging properties, along with in vitro testing using human erythrocytes was examined [118].

Treatment with ozone has been proposed as a method to reduce aflatoxin contamination in peanuts. Ozonation, however, proved to be detrimental to the phenolic compounds present in peanut skins [119]. The peanut skins were exposed to ozonation for an increasing amount of time. The skins were extracted with methanol (80% in water) using sonication as described in a previous publication [40]. After the methanol was removed, the aqueous solution was defatted with chloroform. The extract was then partitioned into ethyl acetate to recover the phenolics. The ethyl acetate was evaporated, and the extract was dissolved in methanol for analysis by HPLC-TOF-MS and total phenolic content using the Folin-Ciocalteu assay. Total flavonoids increased with ozonation time, which was attributed to the disruption of cell walls releasing the compounds from glycosides. The flavonoids and proanthocyanidins were found to decrease rapidly up to 30 min of ozone exposure and then more slowly decrease up to 60 min without being totally lost. Almost total reduction was seen after 60 h of treatment. Correspondingly, the antioxidant activity as measured by the DPPH assay was found to be reduced as well.

Another process effect study subjected peanut skins to gamma irradiation before extraction with methanol alone [120]. This study drew on older research with similar legumes to peanuts [121]. The extracts were used to measure polyphenols using TPC, the amount of condensed tannins, total flavonoids as quercetin, and antioxidant activity using DPPH and ABTS. Only the total flavonoids were slightly increased by the irradiation. The irradiation did not affect DPPH activity but did show dose response with ABTS+. In addition, the stability of soybean oil when the peanut skin extracts added showed only a slight increase over the untreated control regardless of the strength of the

dosage but was much less than the addition of the synthetic antioxidant, BHT. Peanut skins were included in a study of phenolics and their bioactivity of all parts of the peanut seeds and using only methanol as the extracting solvent [63]. In addition to the chemical measurements seen in other studies, this study used the Linoleic Acid Peroxidation System to evaluate the antioxidant assay. The skin extract was found to be the highest in % inhibition of linoleic peroxidation (82.10%), compared to hulls (79.85%), roasted peanut kernel extracts (29.32%), raw peanut kernel extracts (26.57%), and the synthetic antioxidant BHA (88.85%). Pure methanol was also used to prepare peanut skin extracts that were evaluated for their phytogenic properties when added to chicken feed [122]. Levels of 1.0, 2.0, and 3.0 g/kg were added to the diets. A positive dose response was seen in the blood chemistry of the animals as well as a reduction in abdominal fat. Sensory characteristics were not changed.

6. Other Applications

Outside of the use of peanut skins for edible applications, peanut skins have been reported to be carbonized to prepare nanospheres [123]. The skins were subjected to pyrolysis at 700 °C in a nitrogen atmosphere and then oxidized with acid and dried. The creation of nanospheres was confirmed by microscopy and the particles characterized. In the quest to find low-cost applications for this available agricultural waste material, these types of studies are of interest. Use of peanut skins incorporated into nanoparticles to detect a synthetic dye [124]. After sterilization, the peanut skins were extracted with water. The extracts were combined with different precious metal salts under pressure to produce nanoparticles, which were then incorporated into glassy electrodes. These electrodes were able to sense Sudan IV, a synthetic dye that has been used as a food adulterant and is an industrial contaminant in the environment. Extracts of peanut skins prepared using hot water were used to create iron nanoparticles to be used for heavy metal removal from aqueous solutions [125]. A similar application used peanut skin extracts to dye fibers, which were then embedded with silver ions to create nanoparticles [126]. These fibers were used to produce fabrics with antimicrobial properties from a natural source. After evaluating several organic solvents, water was used as the extractant for the peanut skins as that gave the desired color and adequate antioxidant properties for the application. The advantage of these materials is that they are considered environmentally friendly to create and to use. Toxic reagents were not needed, and they were prepared from an agricultural waste product.

To take advantage of the antioxidant properties of peanut skin extracts, they were incorporated into films made from the polysaccharides that make up an Asian mushroom [127]. The gelling properties of the white jelly mushroom (*Tremella fuciformis*) were used to create a biodegradable film. Peanut skins were extracted using 70% ethanol in water and then dried. The powder was incorporated into the gel upon casting. The films did show antioxidant capabilities with the addition of the peanut skin extracts but became more brittle and opaque as the amount of extract was increased over a range of 0 to 100 mg/100 mL of gel. Another study used chitosan as the source of the gel matrix to create a biodegradable packaging film [128]. Starch was chosen as the source of the polysaccharides with chitosan added to adjust the water solubility and flexibility. Extracts of peanut shells and skins were used to add a natural source of antioxidants. The peanut skins were extracted with 80% methanol to determine the antioxidant capacity using the DPPH assay and to characterize the polyphenols present using HPLC-MS. However, the peanut skins were ground to a fine powder and added to the gels to form the films. Extracts of the peanut skins were not used in this case.

7. Negative Aspects of the Usage of Peanut Skin Extracts

The allergenicity of peanuts is a negative factor in the use of any parts of the peanut as a food ingredient. There has been evidence that the main polyphenol in peanut skin extracts, procyanindin A1, has anti-allergenic effects [129]. After purification, this compound was shown to affect the degranulation of cells induced by degranulation downstream of protein kinase C activation or Ca^{2+} influx from internal stores in a rat cell model. This would present the possibility of using extracts from peanut skins as a possible therapeutic agent. A more extensive examination of the protein present in peanut skins

was reported [130]. Of these, 123 different proteins were identified in peanut skins. In addition, 38 of these were unique to the skins and not found in the peanut seed itself. It is thought that many of the skin proteins are expressed in response to stress and serve some role in the defense of the plant seed to insect and fungal attack. To extract these proteins, a lysis buffer was used, followed by precipitation of the protein by methanol to remove the interfering phenolic compounds. However, when the phenolics were allowed to remain with the proteins, the allergenic response was eliminated. This indicates that when the proteins are bound into polyphenols, their ability to bind to IgE sites increases and it elicits the allergenic response. This concept was further studied by using the polyphenol compounds extracted from peanut skin to bind to the protein-binding sites in peanut flour [131]. Water extracts of peanut skins were freeze-dried and then extracted again with 80% ethanol in water and the ethanol was evaporated away. The extracts were mixed with peanut flour which was prepared from roasted peanuts that have been defatted and milled to a powder. After freeze-drying the mixtures, stable aggregates were formed. These aggregates added to rat basophil leukemia cells (RBL-2H3) that had been sensitized with human plasma from a peanut-sensitive individual. The peanut skin extract aggregate was seen to inhibit the phosphorylation of p44/42 of mitogen-activated protein kinase (MAPK) and slightly induced the phosphorylation of p-38. This enzyme is involved in cell proliferation. Blockage of the binding sites was thought to interfere with MAPK signaling by suppressing Ca2+ channeling.

Another issue with the extraction of peanut skins is the concentration of heavy metals in the extracts. Since most of the metals and their complexes are water-soluble, they are concentrated by when using aqueous solvent mixes to recover the phenolic compounds. Using 70% ethanol in water to extract peanuts skins, arsenic and cadmium were found in measurable quantities in the extract after concentration by removal of the ethanol [132]. The study showed that peanut shells can reduce the amount of cadmium by adsorption, but the arsenic levels remained unchanged. The high level of concentration that occurs when peanut skins are extracted can lead to a buildup of heavy metal contaminants in the extracts.

8. Conclusions

The chemical composition of peanut skins has been of interest for over fifty years. Prior to the 1990s, most of the studies have concentrated on the negative aspects of the compounds present. More recently, there has been an increased interest in sustainability in agricultural processes, which has led to more studies for applications of agricultural materials previously considered to be waste, including peanut skins. The polyphenols present in this material are now considered of value. Extraction schemes have become increasingly sophisticated and the studies of their bioactivity have increased to focus more on food applications where peanut skin extracts serve as a nutraceutical ingredient. In addition, the methods and solvents used are becoming more environmentally friendly to allow for these uses and to make the extractions more appealing. The use of green solvent technologies will increase the appeal of making use of peanut skins as a food ingredient and as a nutraceutical additive. As this becomes more widely known, the value of peanut skins will greatly increase. Apart from these solvents, further eco-friendly aspects such as automation of solvent extraction of bioactive compounds from peanut skins will be greatly beneficial [133,134]. This review has tried to cover the current literature with this focus in mind. Table 3 gathers most of the studies discussed in this review to allow the reader to locate those using extractions schemes of interest.

Table 3. Extraction systems used for peanut skins.

First Author (Year)	Market Type	Extraction System	Determination *
Appeldoorn et al. (2009) [69]	Commercial source	Aqueous acetone, methanol	HPLC-MS
Appeldoorn et al. (2009) [33]	Commercial source	Defatted, 20% methanol, column isolation	HPLC-MS, NMR
Attree et al. (2015) [28]	Not stated	Defatted, 70% acetone, acidified	TPC, TFC, CTC, TAC, DPPH, FRAP

Table 3. *Cont.*

First Author (Year)	Market Type	Extraction System	Determination *
Ballard (2008) [47]	Commercial blancher	Range of solvents, optimized to ethanol	TPC, ORAC, HPLC
Ballard et al. (2009) [43]	Virginia	Methanol, ethanol, water	TPC
Ballard et al. (2010) [42]	Commercial blancher	30% ethanol	TPC, ORAC, HPLC-MS
Bansode et al. (2018) [131]	Not stated	Water, 80% ethanol	TPC
Bodoira et al. (2017) [53]	Runner	Defatted, water	TPC, TFC, DPPH
Chang et al. (2020) [50]	Not stated	Defatted, 80% ethanol	TPC, Procyanidins, HPLC-MS, antioxidant activity in cell culture
Chukwumah et al. (2012) [38]	Runner, Valencia	Defatted, 80% methanol, SPE	HPLC-MS
Constanza et al. (2012) [102]	Runner, Virginia	70% ethanol	TPC, ORAC, HPLC-MS
Davis et al. (2010) [67]	Runner	70% acetone, acidified	HPLC
de Carmargo et al. (2012) [120]	Runner	Methanol	TPC, TFC, CTC, DPPH, ABTS, oil oxidative stability
de Carmargo et al. (2017) [74]	Runner	70% acetone, acidified	TPC, ABTS+, DPPH, FRAP, hydroxyl radical scavenging, enzyme inhibition, HPLC-MS
Dong et al. (2013) [70]	Not stated	Defatted, aqueous ethanol, aqueous acetone, column isolation	DPPH, ABTS+, hydroxy radical scavenging, lipid peroxidation in an animal model, HPLC-MS
El-Hack et al. (2018) [119]		Methanol	DPPH, meat characterization
Elsorady et al. (2018) [62]	Local market	70% ethanol	TPC. TFC. TBA. DPPH, HPLC, oil oxidative stability
Francisco et al. (2009) [31]	Runner, Virginia	70% ethanol	HPLC
Fransciso et al. (2009) [52]	Runner	70% ethanol	TPC, ABTS+, peroxyl radical trapping
Franco et al. (2018) [48]	Virginia	75% ethanol, optimized	TPC, TFC, DPPH, ABTS, crocin bleaching, oil oxidative stability
Hoang et al. (2007) [59]	Virginia	Defatted, range of methanol concentrations in water	TPC, CTC, DPPH, metal chelation, HPLC
Hoang et al. (2008) [60]	Runner, Virginia	Hexane, ethanol, ethyl acetate	TPC, DPPH, FRAP, superoxide radical scavenging, oil oxidative stability
Huang et al. (2003) [61]	Spanish	Hexane, ethanol, methanol, ethyl acetate, column isolation	Linoleic acid oxidation, β-carotene, IR, NMR, HPLC-MS
Huang et al. (2019) [30]	Not stated, various seed colors	75% methanol, acidified	HPLC-MS
Jin et al. (2020) [57]	Not stated	Water with surfactant modifiers	TPC, HPLC
Karchesy et al. (1986) [13]	Not stated, red skins	50% acetone, column fractionation	TLC, NMR
Khaopha et al. (2015) [82]	Valencia	Methanol	HPLC, enzyme inhibition in cell culture
Liu et al. (2010) [45]	Not stated	Not defined	DPPH, superoxide scavenging, hydroxy free radical scavenging
Longo et al. (2018) [36]	Local retailer	70% acetone, acidified	HPLC-MS (hydrogen/deuterium exchange
Lou et al. (1999) [18]	Not stated	70% acetone, column fractionation	UV, IR, NMR
Lou et al. (2004) [21]	Not stated	70% acetone, column fractionation	TLC, IR, NMR, HPLC
Ma et al. (2014) [39]	Not stated, red skins	80% acetone, column fractionation	HPLC-MS

Table 3. *Cont.*

First Author (Year)	Market Type	Extraction System	Determination *
Ma et al. (2014) [41]	Commercial blancher	80% acetone	HPLC-MS
Munekata et al. (2017) [104]	Runner	80% ethanol	TPC, ORAC, ABTS+, HPLC, antimicrobial activity
Nepote et al. (2000) [16]	Runner	Methanol	TPC, oil oxidation stability
Nepote et al. (2002) [17]	Runner	Defatted, range of solvents	TPC, DPPH, oil oxidation stability
Nepote et al. (2005) [44]	Runner	70% ethanol	TPC, DPPH
Oldini et al. (2016) [49]	Runner	60% acetone, acidified, column isolation	DPPH, ABTS+, FRAP, NMR
Pominski et al. (1951) [14]	Spanish	Sodium hydroxide solution	Pigment decay, protein determination
Putra et al. (2018) [54]	Not stated	Supercritical carbon dioxide	DPPH, extraction yield
Putra et al. (2018) [55]	Not stated	Supercritical carbon dioxide	HPLC, extraction yield
Rossi et al. (2020) [56]	Runner	60% ethanol	Superoxide radical scavenging, cell toxicity
Sarnoski et al. (2012) [73]	Virginia	Acetone, ethanol, methanol, water, column isolation	HPLC-MS
Sato et al. (2018) [96]	Not stated	Aqueous ethanol, column fractionation	Blood platelet formation in an animal model
Stansbury et al. (1950) [8]	Spanish	Defatted, 95% ethanol	UV
Taha et al. (2012) [66]	Local market	50% methanol, 70% ethanol	TPC, CTC, oil oxidation stability, anticarcinogenic activity in a cell model
Takano et al. (2007) [46]	Not stated	Water, column isolation	Allergenic response in an animal model
Tomochika et al. (2011) [129]	Not stated	Water, column isolation	NMR, MS, enzyme inhibition in cell culture
Tsujita et al. (2014) [84]	Not stated	70% acetone	MALDI-TOF-MS, amylase activity
White et al. (2013) [130]	Runner	Buffer system	HPLC-MS, electrophoresis
Win et al. (2011) [63]	Virginia	Methanol	TPC, DPPH, Linoleic acid peroxidation, HPLC
Yu et al. (2007) [118]	Local market	80% ethanol, column isolation	TPC, HPLC-MS
Zhang et al. (2013) [35]	Retail source	70% acetone, column fractionation	Enzyme assay
Zhang et al. (2014) [119]	Local market	80% methanol	TPC, TFC, TAC, DPPH, HPLC-MS

* Abbreviations used: ABTS+-2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) assay; CTC = condensed tannin content; DPPH-2,2-diphenyl-1-picrylhydrazyl assay; FRAP-ferric reducing antioxidant power; HPLC-high pressure liquid chromatography; IR-infrared spectroscopy; MALDI-matrix assisted laser desorption/ionization; MS-mass spectroscopy; NMR-nuclear magnetic resonance spectroscopy; ORAC-oxygen radical absorbance capacity; TAC-total anthocyanidin content; TFC-total flavonoids content; TLC-thin layer chromatography; TOF-time of flight; TPC-total phenolic content; UV-ultraviolet spectroscopy.

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