RICE HUSK AS POTENTIAL RESOURCE FOR BIOMEDICAL APPLICATIONS: A REVIEW

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Rice husk (RH) is the by-product of the rice milling industry, and its primary disposal via burning can lead to detrimental environmental implications. While literature primarily focused on the potential of its silica component, the cellulosic constituent, which can be of applied value in the biomedical field, appears sparsely reported. Therefore, this review paper critically discusses both the silica and cellulose components of RH investigated for various biomedical uses (adsorbents, drug delivery systems, antioxidant and antitumor activities), and provides the elaborative overview of the chemical extraction methods for both components, while highlighting the needs for optimizing the extraction process for large scale industrial considerations. Discussions on several limitations of the current knowledge that mitigated readiness for biomedical applications (*e.g.* inadequate data from animal studies and clinical trials, as well as the lack of analytical confirmatory tests and non-standardized methods) are also presented. Considering the medicinal properties of RH, the possible utilization of its cellulose content as a new biomaterial for wound healing application is theorized. The information gathered here justifies the use of this agricultural biomass as a new source of economic wealth for biomedical industries, while minimizing the environmental threat that can be associated with its disposal.

Keywords: rice husk, cellulose, fiber, biomedical, wound healing

INTRODUCTION

Rice (*Oryza sativa*) is one of the most important cereal grains worldwide, a staple daily food source for more than half of the world's population.[1] The cultivation of paddy and rice production are pivotal economic activities in the South-East Asian countries, including Malaysia, contributing as a source of nourishment for their ever-rising populations, and accountable for 4.1% of the total agricultural value.[2] Researchers estimated that roughly 2.5 million Asians subsist on rice, and in 2016, Southeast Asia (SEA) contributed to 40% (16 million metric tons) to the world's rice exports, dominated by Thailand and Vietnam.[3,4] In Malaysia alone, around 2.5-2.7 million tons of rice are consumed annually, and the amount is expected to further increase due to rapid population growth.[5] While paddy only occupied 6.9% of the total agricultural land in Malaysia in 1995, the opening of new cultivation fields has increased the total land areas to 9.2% in 2016, creating more jobs for Malaysians, as well as immigrants.[6] Future demand for rice is expected to rise from the already high level of rice consumption as the population continues to grow. The demands for rice have gradually increased among African,[7] the United States of America and South American countries,[8] as well as the European countries and Australia, attributable to the preference change in diet from protein to more fiber- and antioxidant-based meals.[9,10]

The primary process of rice milling involves the removal of the protective husk of paddy for liberating the brown rice grain that contains the endosperm (white rice) and bran.[11]

The increasing demand for this important commodity has resulted in the abundance of rice husk (RH) as by-product.[12,13] It has been estimated that out of 740 million tons of the yearly global production of rice, approximately 148 million tons are of RH, accountable for about 20% of the dry weight of the harvested rice.[14] Malaysia itself produced 408,000 tons of RH by the rice milling industries.[15,16] Due to its presumably very low commercial value, RH is commonly buried underground and/or disposed by open field burning, which can negatively affect the surrounding environment.[6] Although the use of RH to generate steam for powering machineries in rice mills can be economically beneficial,[17] the approach may cause the environmental suspension of crystalline silica particles (*e.g.* quartz and cristobalite), leading to chronic illnesses like silicosis. Silicosis may affect the lungs due to inhalation of silica, which will build up in the lungs and breathing passages, and may lead to scarring.[18,19] Considering its abundance, as well as the detrimental environmental and health impacts that are associated with the current disposal methods of RH, converting this agricultural waste into economic wealth may prove as a prudent approach. In this context, many researchers have deemed the composition of silica and, to a lesser extent, cellulose, as promising for various potential industrial applications.

Being an excellent source of high-grade silica, the combustion of organic components of RH at temperatures between 500° to 700 °C produces the rice husk ash (RHA), which is rich in silica.[20] The harvested silica may prove useful as building material and fertilizer, as well as for composite preparation.[21] Additionally, the cellulose content of RH can also be useful, although it has been scarcely reported in the body of literature reviewed. Cellulose from RH can be extracted via chemical methods involving pretreatment with alkali and bleaching agents.[22] Sodium hydroxide, sulfuric acid, nitric acid and sodium hypochlorite are the typical chemicals used to isolate cellulose and remove the cementing components of hemicelluloses and lignin. The chemical treatments cleaved the amorphous region of the cellulose microfibrils, keeping the crystalline cellulose intact for various potential applications.[23] Hence, the use of RH as the primary source for producing cellulose fibers and nanocrystals proves encouraging. Since research shows that cellulose from RH may have interesting bioactive compounds,[24] its biomedical applications, ranging from adsorptive properties of RH to metal nanoparticles,[25] adsorbents for removing toxicants,[26] antioxidant[27] and anti-tumor agents,[28] as well as drug delivery systems,[29] are worth exploring.

The biomedical industry provides the equipment, technology and medicines to the healthcare providers for offering the best diagnostic, care and treatments for patients.[30] The increased global population and incidence of chronic diseases, as well as escalating research expenses, competition and disease complexity, have put unprecedented strain on biomedical companies' raw material supplies. The higher demand for wound dressing materials has triggered biomedical scientists to explore the possibility of utilizing natural cellulose from the different biomass wastes.[31] Wound dressings produced from cellulose have the potential to fulfil the characteristics of an ideal wound dressing, as these are natural materials that can form a network in which water can be retained.[32] This property helps to keep the wound environment warm and moist, which is optimal for wound healing.[33] Some studies have found that some nanocellulose materials have been able to shorten healing times.[34,35] However, similar attempts at utilizing cellulose harvested from RH as raw material for wound dressing materials has not been reported. Interestingly, the fact that cellulose from RH may confer superior breathability, wettability, as well as enormous antioxidant[36] and anti-tumor activities,[37] its potential use for producing wound healing materials deserves biomedical consideration. Moreover, owing to the high surface area following chemical activation with phosphoric acid (H_3PO_4) and zinc chloride ($ZnCl_2$), the use of RH for removing toxicants (*e.g.* lead) in aquatic system has also been empirically supported.[38] The fact that studies have shown that biogenic silica (SiO_2-rice) is exhibiting similar adsorption–desorption behavior to mesoporous silica, the potential applications of such natural materials for enabling efficient drug delivery systems are advocated.[39]

Having said all the facts about rice and RH, as well as the related biomedical advancements, it is found pertinent to review all the relevant current literature to provide better insights into the properties of RH, favorable for biomedical applications. While the utilization of RH as a potential source of silica for biomedical materials has been largely reported, the same for its cellulose contents remains sparse. This review article is therefore aimed at discussing not only the silica component of RH for various biomedical applications, but also focusing on the currently left out information pertaining to its cellulosic component. The theoretical application of cellulose derived from RH for wound healing biomaterials, as well as the mitigating challenges for such an approach to be utilized are also discussed. As such, this review paper further accentuates the need for utilizing the agricultural biomass for environmental sustainability, as well as creating a new source of economic wealth.

Composition of rice husk

The increasing interest for utilizing RH for various applications has triggered specific interest to understand the chemical composition of such biomass. The chemical composition will provide the information on the % of the cellulose to be utilized. In view of capitalizing on various beneficial compounds from RH, which can be of applied value for manufacturing, industrial as well as biomedical needs, researchers have reported the composition of the inorganic, as well as organic lignocellulosic constituents of RH. It has been reported that silica constitutes a major part of the inorganic component (20%),[40] while cellulose (35%), hemicelluloses (21%), and lignin (31%) are the major organic constituents of RH,[41] the composition of which may vary not only according to the strain and the geographical factor, but also the post-harvest treatment.[42,43] The composition may trigger potential research, especially on the utilization of the lignocellulosic part of the RH, in particular for biomedical applications.

For example, a review by Cheah *et al*. (2016) revealed that analysis results of cellulose, hemicelluloses and lignin for RH from Malaysia, Thailand, India and Taiwan varied considerably. The authors reported that the cellulose, hemicelluloses and lignin contents from RH from those countries range between 31.1-35.5%, 19.4-29.3% and 13.6-26.9%, respectively. Another group of researchers reported wider ranges for cellulose (25%-50%) and lignin (25%–30%), as well as silica (15%–20%) for RH samples analyzed from India, China, and far-East countries.[44] Another recent study reported the percentages of cellulose, hemicelluloses and lignin in RH samples obtained from Jiangsu Province (China) as 35%, 25% and 20%, respectively.[27] In this context, it is pertinent to indicate that while variations in compositions of RH attributable to strains, climatic conditions and geographical location of growth have been generally indicated, specific empirical studies to investigate such aspects in RH harvested from southeast Asian countries like Malaysia remain unreported.[40] The fact that post-harvest treatments can also lead to such variations, further research focusing on this matter appears relevant.

Interestingly, the review of literature reveals those studies focusing on the compositions of RH utilized varying extraction methods, leading to substantial variations in compositions that researchers reported. These aspects further render difficulties in making suitable comparisons among the different results reported by these pertinent researchers to understand the real potential of RH.[40,16,20] Nevertheless, most studies reported about the compositions of RH prior to the different treatments applicable to industrial setup; only one study performed by Johar *et al*. (2012) reported the varying compositions of cellulose, hemicelluloses and lignin, as well as silica, following acid and/or alkali treatments. As a perspective, industrial processes would benefit from the steady supply of good quality RH for the players to maximise its economic value. In this regard, having the standard and optimized extraction conditions may prove useful for enabling the achievement of acceptable yield of cellulose and/or silica for potential applications, since it may not always be possible to acquire RH that are of the best quality for large scale productions.

Extraction of silica from rice husk

Purified amorphous nano-silica has been commonly extracted from RH and fully utilized in various fields as adsorbents, in drug delivery systems, for pharmaceutical and polymer material industries.[45] Hence, the increasing importance of silica leads to a variety of approaches for its synthesis. Chemical treatments with various acids and alkalis were performed, resulting in purified nano-silica.[46] Researchers have therefore adopted various chemical treatments with different variables to derive purified nano-silica.

Sankar *et al*. (2016) extracted nano-silica from RH in two sequential steps: (i) conversion of RH into rice husk ash (RHA); and (ii) formation of amorphous silica. They used incineration process at 700 °C to synthesize the nano-silica. The morphology of the synthesized silicon oxide

(SiO_2) revealed spherical nanoparticles with uniform surface morphology with uniform particle size. The properties of the extracted silica are tabulated in Table 1.

Liou *et al*. (2011) studied the effect of different experimental variables on silica production from RHA. The results revealed that silica pre-treated with hydrochloric acid possesses higher surface area than that subjected to sulfuric, oxalic, and citric acid treatments. Based on the results in Table 1, the optimum conditions for producing silica from RHA are: gelation pH3, silicate concentration of 0.15M, an aging temperature of 50 °C and aging time of 12 hours, with purity of 99.48%.

Table 1
Extraction of silica from RH by chemical treatments

Study objective	Extraction methods used	Main results	Refs.
To synthesize nano-silica from RHA by chemical treatment combined with calcination	• Combustion of rice husk • Acid treatment • Incineration at 700 °C under atmospheric conditions for 2 h	• Spherical morphology with completely amorphous silica particles • Comprising only Si and O	47
To study the ideal conditions for obtaining purified silica	• Washing of RH with distilled water • Acid treatment • Incineration at 500, 600, 700, 800 and 900 °C for 2 h under atmospheric conditions	• Completely amorphous silica • RH sample treated with HCl acid produced purified silica (99%) at 600 °C	48
To study the effects of experimental variables on the characteristics of samples to optimize conditions for obtaining nano-silica	• Washing of RH with distilled water • Acid treatment • Incineration at 700 °C • Alkali treatment • Precipitation	• Optimum result with pH 3, silicate concentration of 0.15M, aging time of 12 h at 50 °C – silica obtained with 99.48% purity	49
To study the effectiveness of acid leaching of RHA prior to alkali treatment and washing the silica obtained with distilled water	• Acid leaching • Alkali treatment • HCl precipitation • Rinsing with distilled water	• Initial acid leaching step did not improve the purity of the silica • Washing step reduced the level of Na and K • 1N NaOH resulted in excellent silica synthesized from RH	50
To optimize the conditions for the preparation of highly purified rice husk ash (RHA) for silica extraction	• Washing of RH with distilled water • Acid treatment • Incineration at 500, 700 and 1000 °C • Alkali treatment • Precipitation	• Purified silica (98.8%) was obtained in almost completely amorphous form (99.9%), with high surface area and reactivity	51
To study the effect of different white rice husk concentration on particle size	• Heated acid treatment • Washing of RH with distilled water • Thermal treatment at 600 °C • Alkali treatment • Neutralization • Precipitation	• Completely amorphous silica ranging from nanometer to micrometer • Particle size increased with increasing concentration of white rice husk • Increased temperature and water reduced the size and modals of silica particles	52

In another study, Bakar *et al*. (2016) extracted silica particles from RH by the acid treatment method. The combustion of unleached, hydrochloric acid-leached and sulfuric acid-leached RH was performed at different temperatures to compare and evaluate the optimum conditions to synthesize purified silica. The authors reported that purified amorphous silica, with purity above 99%, was synthesized from RH by hydrochloric or sulfuric acid leaching, followed by controlled combustion at 600 °C. The purified amorphous silica has large Brunauer-Emmett-Teller (BET) surface area, which might be useful as an adsorbent for various biomedical applications.

To summarize, since there are various extraction approaches conducted by researchers, optimizing the extraction methods has acquired significant attention for efficient and economical ways of extracting optimum amounts of purified silica from RH for potential industrial utilization.

Extraction of cellulose from rice husk for its potential utilization

RH is a lignocellulosic material derived from agricultural waste and often considered a waste product of rice milling, and thus, burned in air or dumped on wasteland.[53] Therefore, many attempts have been carried out to find possible alternative utilization for RH, considering its abundance and composition. Hence, several researchers have extracted cellulose from RH[54,28] and rice straw.[55] The extraction of the cellulose comes from various types of lignocellulosic matrices; it involves a series of processes that are carried out through the break-up of the lignin-cellulose complex by pretreatment and delignification techniques, without the destruction of the cellulose fibrils.[28] The properties of the cellulose extracted are tabulated in Table 2.In recent years, there has been a remarkable interest in cellulose fibers for various applications, including in textile industry,[58] as chemical filters,[59] in fiber-reinforced composites,[60] and for medical applications as well.[61] Hasan and Saoudi (2014) successfully extracted cellulose from several wastes, such as RH, sugarcane and waste office paper, by chemical treatments with acid and alkali, followed by a characterization process. Then, the FTIR spectrum of the extracted cellulose from RH was compared to standard commercial cellulose, proving the removal of the cementing material. X-ray diffraction showed increased crystallinity of the cellulose following the chemical treatments, making it suitable for potential industrial applications.

In another study, Johar et al and Onaja *et al*. (2012) demonstrated that applying bleaching agents, following chemical treatments, affords high purity cellulose. The researchers used different chemical treatment approaches, but reported that by applying bleaching treatment, the general morphology of the bleached rice husk changed from brownish to white, which disturbed the phenolic group in lignin and resulted in the removal of lignin from the RH. Then, acid hydrolysis treatment was performed to obtain nanocellulose, followed with the characterization analysis to confirm the removal of the non-cellulosic component.

Table 2
Extraction of cellulose from RH

Study objective	Extraction methods used	Main results	Refs.
To extract cellulose from several wastes RH, waste office paper and sugarcane)	• Acid pretreatment • Alkali treatment • Filtration using suction filtration • Titration • Washing	Sufficient removal of lignin and hemicelluloses confirmed by FTIR. The crystallinity index of extracted cellulose was 42.3 and 47.7, respectively	56
To extract cellulose fibers from RH by alkali and bleaching treatments	• Alkali treatment • Bleaching treatment • Acid hydrolysis	Analysis confirmed the removal of lignin and hemicelluloses. The chemical treatments enhanced the crystallinity of cellulose and improved thermal stability	28
To synthesize nanocellulose from RH for potential value-added products	• Washing with distilled water • Alkali treatment • Acid hydrolysis • Bleaching treatment	Characterization analysis confirmed the removal of lignin and hemicelluloses. The size of synthesized nanocellulose was around 8-25 nm	57
To isolate cellulose microfiber from RH	• Washing with distilled water • Alkali treatment • Acid hydrolysis • Sonication	FTIR spectra confirmed the removal of cementing hemicelluloses and lignin. The size of the synthesized cellulose micro-sheet was around 180-250 nm	13

The extracted cellulose from RH can be further treated to acquire nano- and micro-features. Shukla *et al*. (2015) isolated cellulose from RH and further micronized the extracted cellulose to micro-dimensions under ambient conditions. The obtained cellulose was then characterized to confirm the removal of the non-cellulosic components and to observe the morphology of the cellulosic microfibrils.

Despite the numerous approaches to produce and purify cellulose from RH, specific attempts to optimize the cellulose extraction method remain limited. Optimization will provide significant information on the extraction parameters to ensure the high quality of the extracted cellulose for various applications, with an acceptable yield of cellulose for large scale production.

PREVAILING APPLICATIONS OF RICE HUSK AS BIOMATERIAL IN BIOMEDICAL RESEARCH

Anti-tumor activities of rice husks

Cancer refers to the abnormal malignant growth of body tissues or cells that occur on any part of the body.[62,63] According to the World Health Organization (WHO), cancer is one of the leading causes of morbidity and mortality worldwide. It is accountable for approximately 14 million new cases and more than 8 million cancer-related deaths in 2012 alone, and the incidence is expected to escalate to more than 70% within the next two decades.[64] To improve the prognosis, accurate clinical diagnosis is essential for prescribing precise and effective treatment, since every cancer type requires a specific treatment approach.[65] Hence, cancer treatment and prevention has been the major focus area in biomedicine: surgery, chemotherapy, radiotherapy, and targeted therapy being the pertinent aspects of treatment.[66] Cancer chemoprevention involves the use of natural, synthetic, and/or biological agents to delay, inhibit, or prevent the initial phases of carcinogenesis, as well as the progression of premalignant cells into malignancy.[28] Although current chemotherapy drugs could potentially inhibit the growth of cancer cells, they exert many adverse side effects, largely attributable to non-specificity of the drugs on cancer cells; the same remains true for radiotherapy.[67] Hence, additional remedies to maintain and improve the health of patients may be required to ease the unwanted side effects experienced by patients upon chemotherapy and/or radiotherapy regimens.[68] For instance, anticancer therapy could be potentially enhanced by using naturally derived compounds from medicinal plants that exhibit antitumor properties.[69,66,70,71] Anecdotal evidence has been suggestive towards the use of numerous plants for treating various types of cancer, as well as alleviating side effects that are associated with the use of conventional chemotherapeutic agents.[72,73] To elucidate this aspect, a great deal of empirically supported bio-prospecting studies for assessing the real potential of such plants for anti-cancer and chemoprotective properties has been reported.

Kim *et al*. (2007) reported the antitumor activity of presumably momilactone B from the methanolic extract of RH on human colon cancer cells (HT-29 and SW620), as well as in Fischer 344 (F334) rats during their *in vitro* and *in vivo* studies, respectively. Momilactone B is an allopathic phytoalexin involved in weed resistance of rice. Their results revealed that the inhibitory effect of the methanolic extract of RH on the proliferation of HT-29 and SW620 cells was dose-dependent, while reducing the frequency of preneoplastic aberrant crypt foci in the colon of F334 rats by 35% when compared with that of controls. Aberrant crypt foci (ACF) are a type of potential preneoplastic lesion that may be the first morphological sign of colon cancer. While the results reported appear promising, the fact that the authors did not use confirmatory analysis, such as GC-MS or HPLC-MS, as well as the standard compound, the accuracy of the identity of momilactone B as claimed cannot be fully supported. Therefore, further analytical confirmatory tests must be performed before the real potential of such a compound from RH can be fully elucidated. Lee *et al*. (2008) evaluated the anticancer potential of unspecified purity of momilactone B extracted from RH on human lymphoma cells (Jurkat cells). The findings suggest that momilactone B at micromolar doses exhibit antitumor efficacy by inducing apoptosis in several blood cancer cells, including human leukemic T cells. The fact that the quality of momilactone B is not reported by this study, the lack of such description would render difficulties for other researchers to replicate the same experiment, necessitating further clarification on this aspect.

To elucidate the possible mechanism of the induction of apoptosis by momilactone B extracted from RH from Korea, Joung *et al*. (2008) utilized two different breast cancer cell lines (MCF-7 and T47D) in hypoxic condition. While reporting on the potential of momilactone B as an anti-cancer agent, as well as postulating on its possible mechanism (*i.e.* suppressing the hypoxia-induced increases of cyclin D1), the authors[74] also indicated that "further *in vivo* studies are needed to establish the mechanism of momilactone B as an anti-breast cancer agent". The authors further indicated the possible chemopreventive or therapeutic ability of the agent for breast cancer treatment, a matter of importance for future scientific endeavor.

Since 2008, the review of literature does not reveal any specific study focusing on the antitumor activities of RH *per se* as well as momilactone B. In this context, Tan and Norhaizan (2017) reviewed the available literature preceding 2009, the gist of which is discussed below. While acknowledging the RH extracts as potential chemotherapeutic and chemopreventive agents, the authors also indicated that "the bioactivity of rice and its by-products is still incompletely understood". Furthermore, while reviewing the preclinical empirical data derived from the limited *in vitro* and *in vivo* studies available pertaining to antitumor activities of RH, it became eminent to the authors that further studies involving the different animal models and human clinical trials may prove necessary before the use of RH extracts can be medically suggested.

Huang *et al*. (2005) reported the potential of Isovitexin extracted from RH as a potent antioxidant that inhibits the tumor necrosis factor α (TNF-α) and cyclooxygenase-2 (COX-2) in a dose-dependent manner by using Lipopolysaccharide (LPS) activated mouse monocyte–macrophage cell line RAW 264.7. Their results revealed that the inhibition of α (TNF-α) and COX-2 is likely due to the antioxidant and anti-inflammatory properties of isovitexin. Although the data derived from *in vitro* studies conducted supported for the use of the compound for its antitumor activity, without proper animal and human studies, the findings are academic alone.

Chariyakornkul *et al*. (2019) investigated the cancer chemopreventive activities of two different colors of RH using *in vitro* and *in vivo* models. A bacterial mutation assay using *Salmonella typhimurium* strains TA98 and TA100 was performed; the enzyme induction activity in murine hepatoma cells was measured, and a liver micronucleus test was performed in male Wistar rats. It significantly decreased the number of micro nucleated hepatocytes in AFB1-initiated rats. Purple RH extract exhibited potent cancer chemopreventive properties *via in vitro* and *in vivo* assessments, ameliorating Aflatoxin B1-induced micronucleus formation in rat liver *via* modulation of some xenobiotic metabolizing enzymes involving in Aflatoxin B1 metabolism. The authors attributed vitamin E and phenolic compounds including anthocyanins as antimutagens for the observation reported for the purple RH. In this context, assessing Single Nucleotide Polymorphisms (SNPs) may prove appropriate for studying the genotoxicity as well as mutagenicity of the white RH and purple RH extracts for providing better insight into the molecular level of mutations.

Rice husk as a source of natural antioxidants

Oxidative stress in biological systems is defined as a complex process characterized by an imbalance of free radicals' production. The elimination process of these reactive chemical species is done by using endogenous and exogenous antioxidants.[75] Human antioxidant defense systems include endogenous (products of the body's metabolism) and could be enzymatic or non-enzymatic. On the other hand, exogenous antioxidants, which enter the body through the diet can be found in specific foods or supplements containing antioxidant formulations, as well as co-factors such as copper.[76] A free radical is capable of independent existence; it contains an unpaired electron in its atomic orbital, making it unstable and highly reactive constituting a causative or associated risk factor for several human diseases, including chronic complications, such as cardiovascular diseases (CVD), cancer and neurodegenerative diseases.[77] Free radicals can either donate or accept an electron from other molecules, therefore behaving as oxidants or reductants.[78] To curb the severity of oxidative stress, the use of antioxidants (substances that delay or inhibit the oxidation of a substrate) to reduce damages of cellular components by scavenging the free radicals, has been suggested.[79,80] Apart from the health aspect, free radicals can also cause lipid peroxidation, which is one of the major reasons for spoilage in food and pharmaceutical products during processing and storage.[81] In this regard, the presence of antioxidant compounds such as tocopherols may potentially increase the shelf-life of such products by acting as scavengers for the free radicals.[75]

Polyphenols are bioactive secondary plant metabolites with antioxidant and anti-inflammatory properties commonly found in RH.[82-84] Also, there are various phenolic compounds in RH, including isovitexin, phytic acid, vanillic acid, syringic acid and ferulic acid, which can act as antioxidants due to the presence of aromatic phenolic rings that can stabilize the unpaired electron.[85] These compounds that can be extracted from RH can potentially be utilized not only for medicinal purposes, but also as food additives, food preservatives and in bio-packaging.[86,87] Owing to such properties, as well as the needs to safeguard the environment, the recovery of polyphenolic substances from agricultural wastes such as RH has become an eminent area of research, converting them into a new economic wealth resource that can create jobs and added value products, especially for biomedical industries.[88] Interestingly, the fact that RH has been reported to contain high contents of phenolic acids, the use of its cellulose component for producing wound healing materials merits scientific considerations. The presence of natural antioxidants may render the RH cellulose a better candidate for producing wound healing materials, as opposed to the current usage of artificial fibers. However, this aspect remains unexplored in the existing body of literature.

Climate effect on the quality of RH as a source of natural antioxidants

It has been indicated that the quality of crops, such as paddy, can be substantially influenced by many biotic (seasons, distribution of rains, soil types) and abiotic factors (irrigation, fertilization, harvesting), producing varying compositions of phytochemicals, even within the same harvest.[89,90] Even though studies focusing on the antioxidant properties of RH have been reported, the evaluation of such biotic and abiotic factors on the composition of the antioxidants, as well as other medicinal compounds, remains sparse.[91] Goufo and Trindade (2015) indicated that, before harvesting the rice, the determining factors for the quality of its antioxidants included soil type, atmospheric CO_2, chemical inputs, temperature, and degree of ripening. Despite such indications, the major factors considered by the other researchers were limited to temperatures, soil types and growth stages alone. Interestingly, Goufo and Trindade (2015) further revealed that the phenolic contents of RH can be markedly reduced with elevated temperatures; however, specific studies focusing on RH in the hot and humid countries, such as Thailand, Vietnam and India, remain unreported. The fact that these countries are among the major producers of rice, evaluating the antioxidant properties of rice and RH produced there may reveal the real medicinal benefits of the commodity and/or biomass.

The effect of different soil types on the composition of antioxidant compounds in RH has been discussed.[82] The phenolic acid composition, c-oryzanol and tocopherols content, as well as their antioxidant capacity, in four fractions of rice (rice bran, RH, brown rice, and milled rice) was analyzed at different growth sites.[82] The results revealed that samples from Suwanaphum district that had "poorly drained, coarse-textured and salt affected" soil type demonstrated better antioxidant capacity.[83] These findings revealed that RH is a valuable source of phenolic compounds, and the authors attributed the observed varying antioxidant activities to the different growth sites and grain morphology. In another study, Kim *et al*. (2011) evaluated the biological activities of the ethanolic extracts of RH samples from nine rice cultivars in Korea. It was reported that the RH cultivated from Nokmi had the most effective antioxidant activities (DPPH radical scavenging activity of 58.46%), when compared with other RH extracts (26.81-44.93%). The fact that the different temperatures and soil types have been shown to affect the quality of the antioxidant properties of RH, and since these factors are often underreported by many authors, specific emphasis in subsequent publications may be required for enabling suitable comparisons. While reviewing the work reported by Kim *et al*. (2011), it was found that the authors suggested the antioxidant activities, without using the analytical methods to speciate and identify the active compounds in the RH. Since studies covering the assessment of antioxidants in varying types of rice, as well as geographical origins and seasons, are very limited and/or outdated, specific attempts to elucidate this aspect in RH harvested from tropical countries, such as Malaysia, is necessary. Moreover, the fact that previous researchers conveniently analyzed the antioxidant properties of RH sampled from the rice distributors, without considering the real geographical attributes (*e.g.* soil types and environmental conditions), further studies involving direct samples of RH from the cultivars may provide better insights on the influences of geographical factors on its antioxidant activities.[92]

Variations in antioxidant activities have also been associated with the different growth stages of paddy.[93] Butsat *et al*. (2009) studied the radical scavenging properties and total phenolic contents in Thailand's RH during five growth stages during grain development. The phenolic acid profiles of RH during grain development were monitored from the flowering stage to the fully ripe stage. Ferulic acid was the major soluble phenolic acid found in all husk extracts during the development stages, accounting for 18-44% of total phenolic acids, with p-coumaric being the main bound phenolic acid of RH (approximately 70-78% of total phenolic acids).[83] While it is interesting that the authors reported about the highest amounts of antioxidants during the flowering stage and the lowest during maturity, the practical value of this information may be limited. This is because RH is abundantly recovered after harvesting the rice during maturity in real agricultural perspective, and it is not sensible to collect RH during the flowering stage.[94] However, the authors did not provide suitable justification for such preference.

In addition, the review of literature reveals scarce information related to the effects of organic farming on the antioxidant composition of rice; however, the available evidence suggests that higher concentrations of antioxidants can be found in organically cultivated rice than in conventionally grown.[95] Previous researchers reported considerably higher amounts of tocopherols and tocotrienols, as well as g-oryzanol, in rice bran and brown rice, respectively.[96,97] Phytic acid content was also higher in organic rice than in conventional rice.[98] Further comparison studies on RH from the different strains cultivated organically may be required to verify such a proposition.

Effects of harvesting and extraction methods on RH as a source of natural antioxidants

The post-harvest treatments that include drying, parboiling, storage, irradiation, milling, stabilization, soaking, germination, fermentation, boiling, steaming, roasting, baking and extrusion may prove necessary to produce the edible final product of good quality rice.[36] Although the fact that these treatments can lead to variations in the antioxidant properties of rice and RH, specific research on this aspect pertained to only Far Infrared (FIR) irradiation. Lee *et al*. (2003; 2004) evaluated the antioxidant activities of organic (hexane, chloroform, ethyl acetate, butanol, and water) extracts of RH samples irradiated with FIR and that of non-irradiated ones.[99,100] Their results revealed that FIR irradiated RH has higher antioxidant activity than that of non-irradiated samples. While reporting a higher amount of cinnamic acid (a well-known antioxidant phenolic compound) than that from non-irradiated samples, they did not report on the use of standard compounds. In addition, the percentage similarity used for confirming the identity of compounds was not provided. The insufficient information that prevailed pertaining to the spectral identification of compounds somehow renders considerable uncertainties in the quantitative interpretation. Notwithstanding, a comparison between pre- and post-harvest compositions in Malaysian produced rice as well as RH has not been reported. Therefore, further studies exploring the different regimens of treatment during storage, covering the different types of Malaysian RH, are required for revealing the suitable dosages that yield the best antioxidant properties for the local products.

An important fact to be accentuated here is that the yield and antioxidant activity of natural extracts were strongly dependent upon the solvent used for extraction due to the difference in polarity of each compound. For example, Lee *et al*. (2004) reported that the polyphenols that they extracted have the strongest antioxidant activity when compared with those of other organic solvents, while the chloroform fraction had the lowest total phenolic content. The fact that various researchers utilized different extraction solvents for reporting the antioxidant properties of RH, suitable 'apple-to-apple' comparison can be difficult to be attempted. Considering that the different extraction methods would result in varying amounts of antioxidants in RH, optimizing the reaction conditions for its large-scale production for pharmaceutical applications appears undeniably important from the economics point of view. To date, optimization studies pertaining to the extraction of antioxidant compounds from RH have not been reported and may prove as a novelty for investigation.

While *in vitro* studies supported that RH may contain enormous amounts of antioxidants and to an extent demonstrated anticancer activities,[27] specific attempts to evaluate such properties in a complete hierarchy of animal models has not been reported. The fact that the available *in vitro* studies on RH limit certain biological aspects in real organisms, specific research to elucidate such activity in an *in vivo* setup appears imperative. Should the cellulose and/or silica from rice husk be used for any biomedical applications involving human (*e.g.* as wound healing materials), the real medicinal value of their antioxidant properties must be tested *via* animal studies and clinical trials, otherwise they are of academic value only and limited to laboratory experiments alone.

Rice husk as biomaterial for drug delivery systems

Drug delivery is the method or process of administering pharmaceutical compounds to achieve a therapeutic effect in humans or animals.[101] RH has been applied in drug delivery systems and silica extracted from RH is known as SiO_2-rice.[29] These SiO_2-related substrates, called biological silicon or bio-silica, possess very low toxicity, and can be utilized in various biomedical applications, including in drug delivery systems. Silica nanoparticles have numerous potential applications, such as biogas and biofuel through anaerobic digestion and lipid extraction, respectively. Interestingly, silica provides a potential toolbox as a raw material for various utilizations due to its biocompatibility and bioactivity.[102] Furthermore, biogenic silica is an excellent alternative to synthetic silica due to its variable structure, density and composition. Among the numerous agricultural bioresources available, RH appears to be a cost-effective bio-precursor for biogenic silica nanoparticle synthesis.[102]

Suttiruengwong *et al*. (2018) evaluated the preparation of mesoporous silica by using a green solvent and renewable sources from rice husk ash (RHA) in the presence of glycerol for potential utilization as drug carrier.[103] Mesoporous silica is silica with porous structure that is capable to absorb or encapsulate relatively large amounts of bioactive molecules. The authors selected ibuprofen as a drug model for the adsorption study and it was reported that the percentages of ibuprofen loading of TMMS (trimethylmethoxysilane) modified mesoporous silica (TMMS-g-MS) was six times lesser, when compared with mesoporous silica aged for 24 hours (MS-24h) due to the hydrophobic nature of the modified mesoporous silica. Furthermore, the release rate of ibuprofen-loaded MS-24h was much faster than that of ibuprofen-loaded TMMS-g-MS. MS-24h appears as more favorable for the adsorption and desorption of ibuprofen than that of TMMS-g-MS. Further treatment of prepared mesoporous silica using TMMS to obtain the hydrophobic mesoporous silica did not appear to confer better adsorption and desorption of ibuprofen than that of mesoporous silica aged for 24 h alone. Hence, the fact that the different drugs would have different pharmacokinetics and pharmacodynamics, such aspects covering the different types of drugs are yet to be proven. Such a proposition also accentuates the need to perform suitable empirical animal and human studies before its real potential can be realized. Further studies to mimic the real GIT absorption of the drugs are necessary to reveal the actual applicability of the drug delivery system.

In another study, Ooi *et al*. (2016) studied the potential use of cellulose nanocrystals (CNCs) extracted from RH as a reinforcing material in gelatin hydrogels and crosslinked with glutaraldehyde for controlled drug release systems. The authors selected Theophylline as a drug model and entrapped it into gelatin hydrogels. A swelling test was done at different pH values to evaluate the effect of pH on the swelling behavior of the prepared hydrogels. The ability of the CNC-gelatin hydrogel to respond to different pH values, along with its high dynamic mechanical stability, suggested that CNC-gelatin hydrogels are promising candidates as drug carriers. However, while the work on the swelling test at different pH values is interesting for drug delivery systems, the range of pH (3–11) that was chosen to mimic the absorption of the drug in the GIT appears peculiar. It is generally understood that the pH of the overall gastrointestinal tract in humans ranges between 1.5–8.5. The fact that the swelling test was not done at pH levels lower than 3.0, as well as without considering the stomach emptying process, the real applicability of the proposed drug delivery system by the authors may prove academic.

In another study, Hernandez *et al*. (2014) evaluated the potential of silica extracted from rice as drug delivery system by using folic acid as drug model. The release profile study was tested at different pH to simulate the physiological conditions of the gastrointestinal tract, with a daily dosage of 400 µg. The findings suggest similar adsorption–desorption behavior of biogenic silica to mesoporous silica, and that the biogenic silica could be an excellent drug delivery system for the folic acid and probably for other drugs. Interestingly, while different drugs, such as ibuprofen, amoxicillin, carbamazepine, Itraconazol and Fenofibrato, have been adsorbed onto the silica matrix, allowing the observation that the inorganic solid could be used as an excellent drug excipient, the same for the biogenic silica remains limited. Although the authors proposed that the biogenic silica could be an excellent drug delivery system for other drugs, the fact that the different drugs would have different pharmacokinetics and pharmacodynamics, such aspects covering the different types of drugs are yet to be proven. Such a proposition also accentuates the need to perform suitable empirical animal and human studies before its real potential can be realized. Rajanna *et al*. (2015) evaluated the preparation of silica aerogel microparticles (SAMs) from RHA for a drug delivery system by using an improved water-in-mineral oil emulsion method. Taguchi design of experiments was used to optimize the parameters. The optimum parameters were found to be 1200 rpm, 1:3 and 5 wt%, respectively. This process yields smaller aerogel particles (mean particle size of 20 µm), with improved properties suitable for drug delivery applications. The efficacy of the improved process was validated by loading a water insoluble drug, ibuprofen, and a food preservative, eugenol, in SAMs. While the use of the optimization method reported by the authors may reduce the amount of wet analysis, the proposed conditions must be validated by an empirical study to evaluate the percentage of deviation observed for the wet analysis, when compared with that of the proposed model. Considering that the authors did not undertake such a validation study, the applicability of the statistical model for real laboratory and industrial applications may be disputed.

Rice husk as adsorbent

Low-cost adsorbents from various agricultural residues, such as RH, have been developed by numerous activation methods and evaluated for the removal of aqueous contaminants. Major benefits of biomaterial-based adsorbents over conventional treatment methods include low cost, high efficiency and regeneration of biosorbents. Agricultural wastes are economic and eco-friendly due to their unique chemical composition, abundance, renewability and high efficiency. Thus, they would be a feasible option for utilization in heavy metal absorption. Agricultural wastes, particularly those containing cellulose, show potential metal biosorption capacity.[104]

According to studies conducted by Chen *et al*. (2011), porous activated carbon (AC) derived from RH, in addition to having wide availability, exhibited fast kinetics and appreciable adsorption capacities.[105] In this review, the mechanism for the preparation of functional AC materials by using a cheap natural precursor – RH – has been discussed. The AC was successfully prepared from RH as activating agent, through heat treatment at different temperatures.[105] The activated carbon derived from RH plays a significant role in adsorption technologies, such as utilization in wastewater treatment for removal of different types of dyes and other organic or inorganic pollutants, such as metal ions (Crini, 2006). The use of RH as adsorbent for removing various toxicants from different media (especially water) has been duly reported in the literature. However, the authors did not attempt to compare the efficacy of this newly developed adsorbent versus that of commercially available devices. As such, the efficiency of such new adsorbents for removing pollutants while reducing BOD is ambiguous.

Cheah *et al*. (2016) reviewed the potential biomedical applications of RH and RHA reutilization into porous nano-materials for adsorption. The activated carbon (AC) derived from RH was produced *via* carbonization and activation of the RH precursor. These processes will result in the development of a porous structure on the AC, increasing the pore volume of the AC.[106] The carbonization process is typically performed at temperatures ranging from 500 to 900 °C, to eradicate the non-carbon elements found in RH, such as nitrogen, oxygen, hydrogen and nitrogen.[107] The pores on the carbonized RH would be further developed by the activation method. The activation method further widens the existing pores by burning off the walls between the adjacent pores and eliminates the disorganized carbon that blocks the pores in carbonized RH. The activation method could be performed through one of the three known methods: physical, chemical or physiochemical activation. Cheah *et al*. (2016) and Bansal *et al*. (2009) revealed that AC prepared from the residue of NaOH treated RH has excellent performance in methylene blue adsorption.[108] The adsorption tests indicated that the AC produced had good adsorption capacity, which was possibly induced by the strong interactions between adsorbent and adsorbate.

However, while the results reported by the author appear promising, it was unclear how much RH is required to prepare a functionally effective unit of AC, and as such the economics of the production can be questioned.

POSSIBLE USAGE OF RICE HUSK CELLULOSE COMPONENTS IN BIOMEDICAL APPLICATIONS – CURRENT LIMITATIONS

Considering the abundance of agricultural wastes (*e.g.* RH) in many developing countries and as studies have shown that such wastes may contain appreciable amounts of useful materials, like cellulose, harvesting them would prove useful. This is a double-edge approach that would be not only beneficial for reducing the amounts of wastes, but also economically and scientifically prudent. Being the major fiber derived from agricultural activities, cellulose is light-weight, renewable and degradable, as well as having low abrasive property, contributing to its possible applications as reinforcing material.[109] Specifically, cellulose harvested from RH is not only thermodynamically stable and crystalline in molecular arrangement with numerous hydrogen bonds.[110] This natural fiber also contains interesting bioactive compounds that can be useful for medicinal purposes.[24,28,29] Hence, the use of RH as the primary source for producing cellulose fibers and nanocrystals for biomedical value-added products is promising, apart from solving the environmental issues relating to the abundance of RH as an unwanted by-product of rice milling activities. Despite its potential benefits and ready availability, studies focusing on cellulose from RH for producing value-added products for biomedically related applications remain very limited, the details of which are discussed below.

Cellulose nanocrystals derived from RH have been studied for possible use in controlled drug delivery systems *via* the production of gelatin hydrogels reinforced with CNCs.[39] The ability of the CNC-gelatin hydrogel to react at different pH conditions, along with its sturdy mechanical stability, suggest that CNC-gelatin hydrogels are promising candidates for controlled drug delivery systems. Oliveira *et al*. (2016) prepared hydrogels from cellulose extracted from rice and oat husks.[14] The cellulose fibers extracted from rice and oat husks showed comparable high purity degree of 93% and 94%, respectively. The findings further revealed that the hydrogel prepared from cellulose derived from RH showed the highest water absorption capacity at 25 °C.

It has to be acknowledged here that plant-based celluloses demonstrated a wide range of mechanical properties and porosities, and the derived cellulose-based materials offer several important advantages over conventional synthetic ones.[111,112] Cellulose-based biomaterials are highly attractive due to the feasibility of modification and control over the features at all levels.[113] The extracted cellulose from RH can be further treated to acquire nano and micro features,[114] apart from the fact that different extraction methods would result in different crystallinities.[98,115-117] Cellulose nanocrystals (CNCs) possessed various desirable properties, such as outstanding mechanical strength, biocompatibility, biodegradability, and high specific surface area.[118] Importantly, the chemical structure of the extracted cellulose could be modified to enhance the properties of the cellulose to cater for the various biomedical applications. For example, collagen hydrolysate was combined with regenerated cellulose and crosslinked with genipin aqueous solutions to further enhance the mechanical properties of the cellulose/collagen hydrolysate (RC/CH)[119] films. The extracted cellulose scaffold derived from RH has complex pre-existing 3D structures that can be altered to suit the application of the biomaterials.[111,120-122]

Interestingly, the extracted cellulose could be fabricated to widen its potential biomedical applications.[120] One approach to improving the mechanical properties of the novel membranes consisting of CNCs extracted from RH is by the compression moulding process, involving polyvinyl alcohol (PVA), glutaraldehyde and glycerine.[123] In another approach, Gupta *et al*. (2019) fabricated cellulose synthesized from RH with starch to increase the tensile strength of the carboxymethyl cellulose and further converted it into a biodegradable film. The cross-linking of starch with CMC molecule increases the intermolecular bonding by introducing covalent bonds to improve the tensile strength of the synthesized biopolymer film.[124] These modifications and enhancement could be a promising approach to be applied on the extracted cellulose from RH for enhanced biomedical applications. Considering the advantages and the possible enhancement of properties that can be done, the utilization of cellulose derived from RH for biomedical applications, especially for controlled drug release systems, wound healing, and tissue engineering appears feasible.

However, such aspects are yet to be proven by extended empirical studies and further pre-clinical, and clinical studies for elucidating their real potential benefits in the biomedical sector, a considerable loophole in the existing body of literature.

Theoretical application of RH cellulose as biomaterial for wound healing – the challenges

Wound healing is a complex series of cellular and biochemical processes, starting with inflammatory reactions, followed by proliferation, and lastly tissue remodeling.[125] When the skin barrier is disrupted by wounds, a series of complex physiochemical processes will occur in an attempt to repair and regenerate the damaged tissue.[126] Based on the duration required for wound healing, wounds can be categorized into acute and chronic.[127] Acute wounds usually heal within eight to 12 weeks after injury, while chronic wounds that include diabetic, pressure, and venous ulcers, are taking more than three months to heal, attributable to local and systemic factors.[128] However, in most cases, the presence of bacteria that contribute to the development of infections is the main cause of chronic non-healing wounds.[129]

The development and application of many interesting wound dressing variants based on natural and synthetic polymers have been actively reported in recent years.[130,131] A promising research direction in the design of wound dressing materials is derived from cellulose extracted from agricultural waste since the materials are biocompatible and biodegradable.[132] As part of the wound healing material, the extracted cellulose would maintain the optimum moisture balance, be capable of controlling wound exudates, and promote wound healing and permeate oxygenation.[133-135] The material can also be painlessly applied and removed, absorbing the products of tissue decay, and serving as an almost insurmountable physical barrier to infection, as well as being comfortable and cost-effective.[135-137]

Modern dressings are designed as carriers to deliver therapeutic agents at the wounded site, while assuming the most varied forms, including hydrogels, films, sponges, foams, as well as electrospun nanofibrous mats.[138,139] Cellulose-based dressings have attracted much attention in the fields of biomedicine, tissue engineering and controlled drug delivery, due to their intricate biomimetic architecture similar to the human extracellular matrix (ECM).[137] This is because the cellulose-based dressing is a potential biopolymer that may imitate the componential and structural properties of the ECM to facilitate cell recruitment. Dressings developed from cellulose isolated from agricultural residues have shown clear advantages over conventional wound dressings, as they act passively during the healing process by simply isolating the wound from the contaminants.[140] They resemble the morphological structure of the extracellular matrix (ECM) of the skin due to their nanoscale features, easily incorporating biomolecules of interest, having high porosity and large surface.[137] Moreover, the demand for materials that are more sustainable, environmentally friendly and cost effective has been acquiring popularity.[141,142] When considering this, biomass-based polymers (*e.g.* cellulose and its derivatives) have become the subject of interest due to their promising properties. Cellulose, being one of the most abundant natural polymers, with relatively easy extraction, superior biocompatibility, non-toxicity and biodegradability, has been considered as a factual option for wound dressing formulations.[143]

The fact that cellulose has high water absorption ability, its role for easy entrapment of exuding wound fluids proves biomedically appealing.[144-146] In this context, variations in physico-chemical properties of cellulose extracted from the different agricultural wastes are generally expected. Surprisingly, while many researchers are focusing on the extraction methodology and characterization of cellulose from RH, empirical research to verify the proposed potential biomedical applications proves at its nascent stage, suggesting more studies on the potential utilization of RH need to be conducted. Cellulose has its desirable attributes (inexpensive, easily fabricated and porous) for treating both acute and chronic wounds, as well as its potential in drug delivery systems (controlled release of therapeutic substances).[147,135,148] However, studies on cellulose derived from RH for wound healing applications are still lacking. Therefore, specific attempts at exploring the characteristics and applicability of cellulose from RH for such medicinal purposes deserve consideration.

Nevertheless, there are challenges in the mechanical properties of the extracted cellulose and processing of nanofibers cellulose that hinder the ready application of cellulose from RH for wound healing. It is believed that the strong inter- and intra-molecular interactions originated from hydrogen bonding, and its rigid backbone structure are responsible for its insolubility in most conventional solvent systems, as well as its inability to melt.[149] To address such limitations, the production of cellulose nanofibers via direct electrospinning, using N-methylmorpholine-N-oxide (NMMO), lithium chloride/ dimethylacetamide (LiCl/DMAc), or ionic solvents, such as 1-ethyl-3 methylimidazolium acetate 1-ethyl-3 methylimidazolium acetate (EmimAc), may prove useful to be potentially utilized as wound dressing for treating acute and chronic wounds.[150] Drugs, nanoparticles, natural extracts, and/or other molecules (growth factors, hormones, or enzymes) may be incorporated into the wound dressing materials to promote better wound healing. Additionally, the appropriate selection of solvents, and the combination of polymers and pretreatments are needed to increase the solubility of the extracted cellulose for further applications. Moreover, the introduction of new chemical functional groups at the surface for biomolecule binding must be first sorted out to ensure reproducible and effective results for acute and chronic wound healing applications. Furthermore, *in vitro* studies also supported that RH may contain enormous amounts of antioxidant activities. Specific attempts to evaluate such medicinal properties of RH in a complete animal model study have not been reported yet, and may prove necessary for wound healing application. The fact that *in vitro* experiments are laboratory-controlled, limiting certain biological aspects in real organisms, specific research to elucidate such activity *via in vivo* setup appears imperative. Should this type of non-clinical findings be applied for humans, further *in vivo* evaluations using various animal models, followed by human trials, are necessary. To date, all these aspects remain insufficiently elucidated in the body of literature, rendering such understanding as only academic, with no tangible application in biomedicine.

CONCLUSION

The available empirical data are supporting the possible use of RH for various biomedical applications that include adsorbents, drug delivery systems as well as antioxidant and antitumor agents. However, several limitations have been identified, mitigating the readiness of RH for realizing its true potential for biomedical applications. Although many researchers have reported on the antioxidant and antitumor activities of RH, the fact that they utilized varying non-standardized extraction methods and, in several cases, validation/analytical data are not provided, appropriate comparisons of such properties among different authors can be challenging. The lack of standardized and optimized extraction processes, as well as variations observed in the compositions of bioactive compounds due to pre- and post-harvest factors, further render difficulties for the major industrial players to consider RH as a reliable source for producing biomaterials for biomedical applications. An optimized extraction method would be useful for yielding optimum amounts of cellulose and/or silica for various potential applications, especially for large scale productions. Considering that RH contains substantial amounts of cellulose and because this component can be very useful as a material for producing wound dressings, its potential for such biomedical application can be suggested. Having said all these, overcoming such limitations appears imperative for capitalizing the economic and medicinal values of RH for benefiting biomedical industries, while also being a feasible option for curbing environmental issues associated with its abundance from agricultural activities.

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