Sepsis, a condition in which the bloodstream is fighting a systemic infection, is a major health concern in both developed and developing countries. As of 2006, severe sepsis claimed the lives of 1500 people worldwide every day.\(^1\) Sepsis is also considered to be the largest cause of global neonatal mortality, responsible 30–50 % of all neonatal deaths in developing countries. In a study conducted by the National Neonatal Perinatal Database from 2002 to 2003, neonatal sepsis occurred in 3 of every 100 live births in India.\(^2\) Sepsis can be caused by bacteria or other sources and includes illnesses such as meningitis, pneumonia, and septicemia.\(^3\) Hepatic (liver) failure is another major cause of sepsis, and hemoperfusion—a process in which the blood is filtered by passage through a cartridge containing adsorbent particles such as activated charcoal—is a standard way to remove toxins from the blood of patients suffering from this condition.\(^4\)

Research has demonstrated that bamboo can be used to create effective blood purification agents for hemoperfusion. *Phyllostachys pubescens*, also known as Moso bamboo, grows predominantly in China but is present in India as well. After preparation by carbonization and steam activation, bamboo charcoal particles can be formed and bound together with biocompatible chitosan to form bamboo charcoal beads (BCBs). Studies of cell viability, hemolysis, and cytokine secretion from macrophage cells demonstrated the BCBs’ low toxicity levels and the weak

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\(^1\) Hsieh et al. (2010).
\(^2\) Sankar et al. (2008).
\(^3\) Mayo Clinic Staff (2012).
\(^4\) Rahman et al. (2006).
immune response it elicited.\textsuperscript{5} Two views of the bamboo charcoal surface morphology are shown in Fig. 3.1.

Activated carbon is commonly used to remove particular toxins from blood, but the degradation of tiny carbonaceous particulates can endanger patients’ health by obstructing or getting stuck in blood vessels. In addition, current methods run the risk of using activated carbon contaminated with heavy metal from fossil fuels.\textsuperscript{6, 7} However, BCBs biodegrade and do not pose the same contamination threat. Not only are these bamboo-based purifying agents biocompatible, they are low-cost as well, increasing their suitability to the Indian medical environment.

\section*{Bone Repair or Replacement}

With about 1 in 10 deaths in India being caused by injuries, it is no wonder that trauma and orthopedic applications have become crucial to improving the country’s health outcomes.\textsuperscript{8} Bioceramic, metallic, and polymeric biomaterials have all been used to try to address these needs. However, they all face challenges in their application. Bioceramic implants typically exhibit poor resistance against fatigue failure and low fracture toughness, which poses a problem for bone-repairing purposes. Due to their elasticity mismatch with bone, metallic materials will lead to stress-shielding and bone resorption. Polymeric materials possess a low modulus of elasticity, which limits their applications as well.\textsuperscript{9}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{bamboo_charcoal_morphology.png}
\caption{Bamboo charcoal surface morphology, two views via SEM micrograph (Hsieh et al. (2007))}
\end{figure}

\textsuperscript{5} Hsieh et al. (2010).
\textsuperscript{6} Chandy and Sharma (1993).
\textsuperscript{7} Chandy and Sharma (1998).
\textsuperscript{8} Joshipura (2008).
\textsuperscript{9} Li et al. (1996).
As a result, bamboo has emerged as a promising biomaterial for bone repair and replacement applications. Researchers have found that there are many structural similarities between bamboo and human long bones. For example, bamboo has a gradient structure in the radial direction resembling the bone’s gradient structure from outer cortical to inner spongy bone, indicating the potential application of bamboo for bone fracture fixation. In addition, across the bamboo stem (for the bamboo _Phyllostachys bambusoides_), the average modulus elasticity is 18 GPa, which is the same as the value for human cortical bone. Bamboo also has fairly high longitudinal tensile, bending, and compressive strengths, all of which are necessary for a good biomaterial meant to repair or replace a load-bearing bone.10 The fact that bamboo also possesses silicon on the inner and outer surfaces of its stem means that it may have an easier time conducting bone mineralization.11 Plus, studies have shown that the porous nature of bamboo can help with the ingrowth and anchorage of bone.12

One study demonstrated that, owing to its silica components, bamboo is able to induce precipitation of calcium phosphate _in vitro_. This is a particularly significant development because many scientists believe that the formation of such an apatite layer is necessary for a biomaterial to properly bond to bone. After chemically removing surface fatty substances, the researchers grafted the bamboo with a polyethylene glycol-based polymer that can facilitate calcification because its polyether soft segment polymer can cause metal-ion chelation. The grafted bamboo samples were then soaked in one of two calcification solutions: accelerated calcification solution (ACS) or simulated body fluid (SBF). The bamboo then formed continuous layers of calcium phosphate, a major component of human bone. Although the bamboo did possess some cytotoxic leachable components that could pose a threat to patients, they could be largely removed by ethanol, methanol, and toluene.13

In another study, charcoal bamboo (_Bambusa glaucescens_) was specially fired, sterilized, and shaped before being inserted in the resected tibial diaphysis of white rabbits. At 6 weeks, there was neobone invasion into the bamboo’s pores, and good bony ingrowth was seen months later. Another promising finding was that there was no evidence of fibro-encapsulation or inflammatory response in the bone marrow or at the area where the bone and bamboo made contact.14 Therefore, charcoal bamboo was found to be a suitable alternative bone substitute, and future studies should explore potential applications in humans.

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10 Li et al. (1996).
11 Charnot and Peres (1978).
12 Bednar et al. (1982).
13 Li et al. (1997).
14 Kosuwon et al. (1994).
Neuroprotection

Neurological disorders are becoming an increasingly significant problem in Indian health. Based on prevalence studies of common neurological disorders conducted among rural and urban populations in the Bangalore region, some researchers have estimated that between 20 and 30 million Indians suffer from neurological disorders of various sorts. One study conducted in 1987 and replicated in 2004 revealed a nearly five-fold increase in the incidence of Parkinson’s disease over that time period, from 0.07 to 0.33 per 1,000 people.\(^{15}\)

Bamboo has demonstrated the potential to protect against neuronal damage and neurodegenerative disorders—such as Alzheimer’s, Parkinson’s, and Huntington’s diseases—where inflammation and oxidative stress are implicated. A relatively recent development in the effort to combat such diseases is the strategy of attenuating the transduction of apoptotic signals in order to prevent neuronal cell death.\(^{16}\) Studies have shown that one way to go about doing this is to use lignin, a durable network polymer that accounts for 20–30 % of global plant biomass, making it the second most abundant organic plant substance.\(^{17}\) Scientists have devised a system to convert lignin into derivatives including lignophenols, which are very active, stable, and phenolic. These lignophenols demonstrated impressive neuro-protective abilities against oxidative stress-induced apoptosis. In one study, lig-8—a lignocresol derived from bamboo—derived the strongest neuro-protective activity against hydrogen peroxide-induced apoptosis in human neuroblastoma cells. Lig-8 also showed an anti-apoptotic effect by impeding the dissipation of the mitochondrial membrane permeability transition. In addition, flow cytometry revealed that lig-8 exhibited antioxidant properties in the cells exposed to hydrogen peroxide. Therefore, bamboo-derived lig-8 has the potential to be an effective neuro-protector, altering the signaling pathway of neuronal cell death and slowing the progress of neurodegenerative diseases.\(^{18}\)

Another study has demonstrated the potential of lig-8 to protect against neuronal damage caused by several other sources: oxygen-glucose deprivation followed by re-oxygenation, tunicamycin, and proteasome inhibitor. The study examined the activity of lig-8 in two scenarios of oxygen-glucose deprivation (OGD) stress-induced neurotoxicity, which may be related to endoplasmic reticulum stress. The first was in the common neuronal differentiation model of pheochromocytoma (PC12) cells while the second was in vivo against retinal damage-induced mice. The tunicamycin—a glycosylation inhibitor that is cytotoxic to many cells\(^{19}\)—induces cell death in PC12 cells. The proteasome inhibitor (PSI) also induces cell death, but in human neuroblastoma cells. Lig-8

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\(^{15}\) Gourie-Devi (2008).

\(^{16}\) Akao et al. (2004).

\(^{17}\) Ito et al. (2006).

\(^{18}\) Akao et al. (2004).

\(^{19}\) Varki et al. (1999).
demonstrated impressive neuro-protective effects in each case. OGD-induced cell damage displayed an inverse relationship to the concentration of lig-8 applied, with lig-8 at a 30 μM concentration demonstrating the same level of cell viability as the control PC12 cells. Lig-8 also inhibited tunicamycin-induced cell death in PC12 cultures, with the greatest neuro-protective effect occurring at a concentration of approximately 3 μM. Lig-8 treatment also substantially decreased PSI-induced apoptotic cell death in SH-SY5Y cells.

It is likely that lig-8’s neuro-protective abilities are related to lignin’s physiological effects that enable woody plants to live longer than many animals. Lignin in such plants may physically protect plant cells by acting as a glue-like substance while also offering some sort of biological protection. Such potential behavior can be further explored in future studies. Regardless of the outcome of such studies, since the bioactive lignophenols derivative lig-8 demonstrated neuro-protective effects in both in vitro and in vivo models, it is likely that it will also exhibit such abilities when it has penetrated living human tissue.

Banana Applications

Burn Dressing

As of 2004, burns were the 8th largest cause of death worldwide in people aged 15–29 years and 10th largest in people aged 5–14 years. Today, fire-related burns disfigure and disable millions every year while killing hundreds of thousands of others. Low- and middle-income countries bear a disproportionate amount of this burden, accounting for 95% of fatal fire-related burns. The situation is particularly stark in India, where the estimated annual burn incidence is somewhere between 6 and 7 million. It is also likely that more than 100,000 Indians lose their lives to fire-related causes each year. Currently, treating burns can be an expensive process involving hospital stays, costly medications, multiple operations, and extended rehabilitation periods. However, the vast majority of burn victims in India have low incomes, with an average per capita monthly income equivalent to less than $5 a month. This poses an obvious affordability hurdle and has precipitated the search for a cheap but effective dressing alternative.

20 Ito et al. (2006).
21 World Health Organization (2010).
22 Chandran (2010).
23 Ebel et al. (2010).
24 Gupta et al. (2010).
25 Sanghavi (2009).
26 Gore and Akolekar (2003).
One Mumbai hospital used boiled potato peel bandages (BPPB) as an alternative and patients generally preferred them to the original Vaseline gauze dressings. However, there was still some discomfort associated with these bandages and their preparation was too time-consuming and challenging to teach and learn. In addition, although the BPPBs cost less than $1, they were still out of many patients’ price range.\(^\text{27}\)

Large, inexpensive, and easily attainable, the leaves of banana plants were found to address many of these problems. The leaves were cut down their midribs and pasted onto bandage cloth with a flour-based paste before being autoclaved for use in patients along with a topical agent. These banana leaf dressings (BLD) were compared to BPPBs in a 30 patient trial and found to be generally similar or superior. There were no significant differences between the two materials with respect to days taken for epithelialization, eschar formation, the need for skin to graft over deep partial thickness burns, or microbe growth. Images of the banana leaf dressings are shown in Fig. 3.2. Since minimal discomfort was experienced and the BLD was easier to prepare and 1/11th the cost of the BPPB, this banana-based biomaterial proved to be a promising development in the field of burn dressings (See foot note 27).

**Inhibition of Viral Transmission**

As of 2010, approximately 34 million people were living with HIV—over 95 % of whom resided in low- or middle-income countries—and there were over 7,000 new HIV infections every day. AIDS-related causes have claimed the lives of almost 30 million people already, and the virus has deleteriously affected the lives

\(^{27}\) Gore and Akolekar (2003).
of countless others. This global HIV epidemic has not overlooked India. Current HIV estimates in India range from 1.5 to 3 million infected people.

In addition, even though over 25 anti-HIV drugs were approved and availability of antiretroviral (ARV) therapies had been improving in low- and middle-income countries, by 2008, the rate of new HIV-1 infections was 2.5 times greater than the rate of new individuals receiving ARV drugs. An effective HIV vaccine may be many years away and condoms—though useful in combating the spread of HIV—are often used incorrectly or inconsistently, particularly in areas where women have less control over their sexual activity. Therefore, the development of intravaginal or intrarectal microbicides may be a good alternative. In fact, some predict that over just 3 years, covering one-fifth of the population with a 60% effective microbicide could prevent up to 2.5 million new HIV infections.

Several promising HIV transmission inhibitors block the virus before it integrates its genome into the target cell. Lectins—proteins that can recognize and bind carbohydrates without altering them—are able to inhibit the HIV-1 entry step by binding to the viral envelope’s carbohydrate structures. One HIV-1 envelope protein, called gp120, is an attractive target because it contains multiple sites for glycosylation, a process crucial to the viral life cycle. Studies have shown that banana lectin (BanLec) is able to bind to high mannose structures on gp120 to prevent the cellular attachment and entry of HIV. Cells treated with BanLec demonstrated lower levels of strong-stop DNA, an early HIV reverse transcription product that can often be detected between when the virus enters the cell and when the virus is uncoated. In addition, although most of banana lectin’s HIV inhibitory activity derives from its ability to block viral attachment, some HIV inhibition was still observed when BanLec was added after attachment. Therefore, BanLec could also be useful in preventing HIV transmission through post-attachment steps including virus fusion to the cell.

Using BanLec as an anti-HIV agent could also be effective because lectins can hinder the development of resistance by targeting multiple different glycosylation sites on the virus. Research has shown that for resistance to develop, many more mutations in the envelope sequence are needed than are typical. Administering a combination of different lectins would further reduce the chances that a lectin-based anti-viral therapy would fail due to resistance. Even if the virus developed a resistance to BanLec and other lectins, it is possible that this would increase its vulnerability to the normal human immune response. This is because the changes

28 Kaiser Family Foundation (2011).
29 United Nations Development Project, India (2011).
30 Jha et al (2010).
31 Joint United Nations Programme On HIV/AIDS (2008).
32 Swanson et al. (2010).
33 Watts (2002).
34 Meagher et al. (2005).
35 Swanson et al. (2010).
in glycosylation that allow the virus to develop resistance to lectins also increase its susceptibility to neutralizing antibody responses. 36

Studies have shown that banana lectin microbicides have demonstrated the capacity to be as powerful as two major microbicides that have been developed. However, the BanLec treatments are less expensive and do not demonstrate the same side effects associated with those two. 37 Although there are still some safety concerns that need to be explored with BanLec, attaching recombinant therapeutic proteins to the lectin’s polymer chains have been shown to reduce toxicity and alter bioavailability. Banana lectin also has potential antiviral applications beyond HIV. Glycosylation is a process crucial to other viruses as well, not just HIV-1. Particular lectins have already demonstrated inhibitory behavior with respect to viruses such as Ebola, hepatitis C, influenza, Marburg, and SARS coronavirus. BanLec could possibly be applied to combat the spread of such viruses as well. 38

Therefore, banana lectin has exhibited potential to inhibit the transmission of viruses, particularly HIV. Bio-derived applications of this and other lectins should be explored to develop methods to better combat the spread of infectious disease, such as intravaginal microbicides to reduce HIV transmission.

**Diabetes Treatment**

Over the past few decades, the diabetes predicament in India has gotten progressively worse. As of 2007, India was the “diabetes capital of the world” with 41 million Indians having diabetes. This meant that one in five diabetics worldwide was Indian. 39 Predictions for the future do not paint a more optimistic picture, with an estimated 87 million Indians being diabetic by 2030. 40 Hence, there have been massive efforts to find effective treatments for diabetic patients.

The pseudostem and flower of banana plants, as pictured in Fig. 3.3, have been found to be effective in the treatment of diabetic rats. When consumed at a 5% level in the diet, symptoms such as body weight, glomerular filtration rate, polydipsia, polyphagia, polyuria, and urine sugar were all ameliorated. 41 The methanolic extract of one type of banana fruit (Musa paradisiaca) has a hypoglycemic effect on diabetic mice 42 while pectin from a different type (Musa sapientum) had

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36 Swanson et al. (2010).
37 Reed (2010).
38 Swanson et al. (2010).
39 Joshi and Parikh (2007).
40 Joshi et al. (2012).
41 Bhaskar et al. (2011).
42 Ojewole and Adewunmi (2003).
a hypoglycemic effect on alloxan diabetic rats. Hence, banana-derived compounds have demonstrated anti-diabetic effects that should be further investigated to examine potential for therapeutic applications.

**Bone Grafting**

Ligno-cellulosic banana fibers have also demonstrated potential for use in bone grafting substitutes. Banana fiber composites externally coated with calcium phosphate and hydroxyapatite could be useful for the fixation of fractured human bones, both internally and externally. Their biocompatibility combined with their strong mechanical properties could make banana fibers an ideal candidate for bone repair and replacement. In comparison to sisal and roselle fibers, banana fibers have a higher density and modulus of elasticity. Banana fibers are an especially appealing candidate given their current treatment as a waste material, so their incorporation in biomedical applications would put them to good use.

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43 Pari and Umamaheshwari (2000).
44 Chandramohan and Marimuthu (2011).
Gastric ulcers are a painful condition posing an increasing problem to people in both the developing and developed worlds. Affecting 1 of every 20 people worldwide, gastric ulcers are thought to be caused by an imbalance between luminal acid and pepsin on one side and the mucosal layer, phospholipid layer, prostaglandins, and other factors on the other side. Many researchers are currently looking for more effective ways to treat gastric ulcers, which can be caused by such diverse factors as stress, nutritional deficiencies, and nonsteroidal-anti-inflammatory drugs.45

Multiple studies have demonstrated the protective effects that unripe plantain banana extract can have on gastric mucosa at risk for aspirin-induced damage. Therefore, a study was undertaken to examine the anti-ulcerogenic properties of the unripe plantain banana extract and its potentially active ingredient, the flavonoid leucocyanidin. The chemical structure of leucocyanidin is shown in Fig. 3.4. Active banana powder was prepared by drying fresh pulp at temperatures below 40 °C. This study showed that an aqueous, leucocyanidin-rich extract exhibited substantial anti-ulcerogenic properties, even when exposed to artificial gastric juice. The anti-ulcerogenic properties of such flavonoids have been partially explained by their reduction of acid secretion by gastric parietal cells.46 This demonstrates the anti-ulcerogenic potential of banana-based compounds and further exploration of the topic could yield important therapeutic applications for human ulcer treatment.

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45 Rony et al. (2011).
46 Lewis et al. (1999).
Iron Absorption Promoter

As one of the most common forms of malnutrition in the world, iron deficiency is a major global health concern that affected over 2 billion people at the end of the 20th century. Iron-deficiency anemia is a particularly significant problem for women in developing countries like India, where it is a common cause of maternal morbidity and mortality, pregnancy and delivery complications, and child-development problems. In 1990, the Government of India claimed that nearly 1 in every 5 maternal deaths in the country was related to anemia, and 2 years later the World Health Organization estimated that a staggering 88% of pregnant Indian women were anemic. What is perhaps even more troubling is that despite widespread efforts and programs to lower the levels of anemia in India, the prevalence of anemia in pregnant mothers actually increased from 49.7% in 1999 to 58.7% in 2006. This indicates a need for a new approach to anemia treatment.

One promising approach involves the use of inulin, a fructan, from bananas. The chemical structure of inulin can be found in Fig. 3.4. This type of inulin is associated with decreased sulfide concentrations and increased concentrations of soluble iron in the colon digesta of pigs. In addition, the increase in iron absorption was not accompanied by a change in the digesta’s pH or phytase activity, which could have negative effects on other digestive and absorptive properties. Since pigs have a similar anatomy and physiology of the gastrointestinal tract as humans and their iron status can be easily manipulated by iron injection dosages, these animals are a good model through which to study human iron absorption.

Studies have also shown that inulin enhances iron absorption and retention as well as hemoglobin repletion efficiency and hemoglobin recovery from anemia in rats. Therefore, banana inulin-based therapeutics have good potential to reduce iron deficiency in humans and lower the burden of anemia in India.

Coconut Applications

Obesity and Diabetes Treatment

Studies indicate that hyperinsulinemia—a condition in which blood insulin levels are higher than normal for non-diabetics—is closely related to particular pathophysiological changes that occur during the progress of type 2 diabetes,
cardiovascular disease, and cancer.\textsuperscript{52} High glucose levels in the blood can also lead to additional glycation products which might create unwanted functional and morphological alterations.\textsuperscript{53} Since postprandial (after-meal) hyperglycemia in type 2 diabetic patients can lead to complications and diets with high glycemic indices can boost one’s chances of developing cardiovascular disease, insulin resistance, and type 2 diabetes, it has become increasingly important to adequately control blood glucose and insulin response levels to avoid disease development. This has become a substantial problem with the increasing percentage of people who are overweight or obese from excess dietary energy intake, which can induce insulin resistance.\textsuperscript{54}

Coconut is a rich source of D-xylose, a monosaccharide that is thought to suppress the postprandial glucose surge. This could be a very important tool in treatments to combat obesity-related diseases, an area where postprandial hyperglycemia is believed to play a significant role.\textsuperscript{55} This sucrase inhibitor has been shown to lower intestinal sucrose activity by over 50\% in rats.\textsuperscript{56} D-xylose in 5 g and 7.5 g doses has also lessened increases in serum glucose and insulin levels and slowed down glucose absorption in a study of 49 humans.

In one experiment, a control group consumed 50 g sucrose while a test group consumed 5 or 7.5 g xylose in addition to 50 g sucrose. Results showed that serum glucose levels after 30 min were substantially lower among those subjects who were administered xylose. Similarly, after 15 min, mean serum insulin was far lower in the test group. All of this indicates that coconut-derived D-xylose can be used to positively alter the postprandial glucose and insulin response and successfully inhibit the effects of obesity- and diabetes-related conditions.\textsuperscript{57}

With respect to diabetes specifically, coconut has also demonstrated significant anti-diabetic effects. Research has shown that the hydro-methanol extract of \textit{Cocos nucifera} (HECN) exhibited an anti-hyperglycemic effect in streptozotocin (STZ) induced diabetic rats that was comparable to that of glibenclamide, a common anti-diabetic drug. It is thought that HECN’s glucose-lowering abilities might be due to an increase in pancreatic insulin secretion from existing beta cells or release from bound insulin.\textsuperscript{58}

The diabetic rats demonstrated elevated levels of triglyceride (TG) and cholesterol along with decreased HL levels. This could be due to an insulin shortage that activated lipase enzymes to hydrolyze stored TG and release fatty acids and glycerol into the blood. Increased TG and cholesterol in the rats’ blood could result in cardiovascular disease. However, treatment with HECN improved the rats’ lipid

\textsuperscript{52} Bae et al. (2011).
\textsuperscript{53} Gavin (2001).
\textsuperscript{54} Bae et al. (2011).
\textsuperscript{55} Ibid.
\textsuperscript{56} Seri et al. (1996).
\textsuperscript{57} Bae et al. (2011).
\textsuperscript{58} Naskar (2011).
profiles, potentially helping to improve lipid metabolism and avoid diabetic complications. HECN treatment helped restore elevated levels of particular biomarker enzymes indicative of impaired liver function—such as serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and serum alkaline phosphatase (SALP)—to normal levels, indicating decreased diabetic complications. Treatment with HECN also inhibited hepatic lipid per-oxidation levels and boosted liver antioxidant parameters towards non-diabetic levels, thereby resulting in less tissue injury and fewer pathologic complications of diabetes.\(^{59}\) Thus, hydro-methanol extract of \textit{Cocos nucifera} has demonstrated significant anti-diabetic and lipid profile improvement abilities that can be further explored for therapeutic application in humans.

**Helminth Treatment**

Billions of humans and animals suffer from infections of helminths,\(^{60}\) which are multicellular parasitic worms that derive nourishment from their hosts.\(^{61}\) The situation is particularly unfortunate in India, where hundreds of millions of people are estimated to have intestinal nematode infections (nematodes are one type of helminth).\(^{62}\) Two types of helminths commonly found in India are pictured in Fig. 3.5. This massive burden of helminth infection, particularly on the developing world, has spurred investigations of various ways to prevent and get rid of the parasites.

\(^{59}\) Naskar (2011).
\(^{60}\) Mehlhorn (2008).
\(^{61}\) Jaykus et al. (2009).
\(^{62}\) de Silva et al. (2003).
Research has demonstrated that coconut possesses anti-helminthic properties. One study selected naturally infected sheep in three different locations—Egypt, Germany, and Saudi Arabia—to test the anti-helminthic effects of several crops in differing geographies. After being fed 60 g coconut endosperm powder and 60 g onion powder with their food each day for eight days, the animals with gastrointestinal nematodes and cestodes no longer had any worm stages in their feces, as observed on days 9 and 20. Compared to untreated sheep, their body weights also increased substantially, indicating that internal worm reduction was very effective. Hence, coconut has promising anti-helminthic applications that could also be explored in humans.63

**Ulcer Treatment**

Coconut milk has been shown to be an effective anti-ulcerogenic agent. Subcutaneous injections of indomethacin led to ulceration in male rats, and the cytoprotective abilities of coconut water, coconut milk, and sucralfate (a conventional cytoprotective medicine used for treating ulcers) were compared. While coconut water resulted in a 39 % reduction in mean ulcer area, coconut milk resulted in a 54 % reduction, which is nearly the same as the 56 % result produced by sucralfate. The difference between the sucralfate and coconut milk results were not statistically significant, so they are considered to have essentially the same effect. Thus, utilizing properties of coconut milk could prove to be an effective means to treat gastritis and ulceration, and its low cost could be more suited to developing countries like India.64

**Intravenous Treatment**

Coconut water is an excellent option for a short-term intravenous hydration fluid, as demonstrated by studies throughout the world. This is particularly true in many areas of the developing world, where more advanced treatment fluids might be too expensive or difficult to access.65 Found as a free fluid inside the coconut, coconut water is an acidic solution comprised mainly of amino acids, electrolytes, and sugars. Its electrolytic components—rich in calcium, chloride, magnesium, and potassium—are similar to those of intracellular fluid, while its sodium content is

63 Mehlhorn et al. (2010).
64 Nneli and Woyike (2008).
65 Campbell-Falek (2000).
lower than human plasma. Such properties indicate coconut water’s potential application for total parenteral nutrition (TPN) under particular circumstances.

Coconut water has even been used in large volumes as a resuscitating and hydrating intravenous fluid during conflicts ranging from World War II to the Nigerian civil war of the 1960s. Studies have demonstrated its successful use in cases where infusion over the course of 6 to 12 h totaled 3 liters of coconut water. Since green coconut water is usually sterile, it is well-suited to intravenous use, but it can also be used as a culture medium in microbiology and plant biology.

In humans, the coconut water displayed similarities to a hypotonic intracellular fluid, and possessed slightly more than one half of the typical human blood plasma’s cation or anion content. Such high concentrations were found to be quite safe and did not cause any negative coagulation initiation processes. Although coconut water may not be precisely on par with standard TPN solutions, it is a viable low-tech, low-cost solution that could increase health care access if used as an intravenous fluid.

**Jackfruit Applications**

**Protease Inhibitor**

Jackfruit is commonly used in folk medicine and herbal treatments. Diarrhea, dermatosis, anemia, and asthma can all be treated with jackfruit leaves and roots, which can also be used as an expectorant for coughs. Oftentimes, biomaterial and therapeutic applications explore the fruit or leaves of a plant. But since jackfruit is a rubber-producing plant, all parts of the jackfruit tree contain a sticky aqueous emulsion—latex—that also has important medical applications.

From the milky latex of the *Artocarpus heterophyllus* fruit stem, researchers have used heat precipitation and anion exchange chromatography to purify a heat-stable heteromultimeric glycoprotein (HSGPL1) that can act as a protease inhibitor. This protein can alter the human blood coagulation system’s intrinsic pathways by increasing the activated partial thrombin time (APTT) and inhibiting

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66 Pummer et al. (2001).
67 Petroianu et al. (2004).
68 Ibid.
69 Pummer et al. (2001).
70 Petroianu et al. (2004).
71 Eiseman (1954).
72 Pummer et al. (2001).
73 Fernando et al. (1991).
74 Mekkriengkrai et al. (2004).
particular blood coagulation factors, called XIa and α-XIIa.\textsuperscript{75} The process by which human blood clots can be explained via three pathways: intrinsic, extrinsic, and common.\textsuperscript{76} APTT is a way to measure the functions of the latter two pathways, representing how long human plasma takes to clot after an intrinsic pathway activator, phospholipid, and calcium have been added.\textsuperscript{77} In addition, HSGPL1 contributes to the maintenance of homeostasis in cells under both optimal and adverse growth conditions. These glycoproteins can help proteins refold under conditions of stress and they can also assist with stabilizing proteins and membranes.\textsuperscript{78}

\textsuperscript{75} Siripatetawee and Thammasirirak (2011).
\textsuperscript{76} Brown (1988).
\textsuperscript{77} Shih et al. (2010).
\textsuperscript{78} Siripatetawee and Thammasirirak (2011).
Therefore, this jackfruit-derived protein could be extremely useful for the diagnosis or treatment of hemorrhagic or thrombotic conditions. Potential applications for HSGPL1 include treatment for fibrinolysis (which prevents blood clot formation), wound healing, and blood coagulation.\textsuperscript{79} This is especially important given the extremely high cost of many treatments currently offered in the market.\textsuperscript{80}

**Tablet Disintegrant**

Starches derived from jackfruit seeds have potential applications as tablet disintegrants. *Artocarpus heterophyllus* seeds—which are often considered biowaste material— are approximately one-fifth starch on a dry weight basis. This starch possesses characteristics different from many other starches, particularly with respect to acid resistance, granule shape, and thermal and mechanical properties.\textsuperscript{81}

In particular, scientists have found that carboxymethyl jackfruit starch cross-linked with sodium trimetaphosphate (CL-CMJF) possesses some properties suitable for a tablet disintegrant. Sodium starch glycolate (SSG) and croscarmellose sodium (CCS) are two common commercial superdisintegrants used today. The CL-CMJF—which can be produced via a dual, simultaneous reaction involving non-toxic chemicals and solvents—proved to be insoluble in water but demonstrated a swelling ability and uptake profile similar to those of CCS.\textsuperscript{82} Figure 3.6 shows the disintegration patterns of three tablets containing CL-CMJF, SSG, and CCS over a three minute interval.

Thus, it is worth further exploring the applications of jackfruit seed starch for tablet disintegrants, as they may prove to be a more effective and less expensive option than those currently used.

**Leukemia Treatment**

Leukemia is the most common form of childhood cancer in India, accounting for between 25 and 40\% of all such cases. With such a low prognosis that only one-third of leukemia-stricken children in India survive at 5 years, leukemia is also the country’s largest contributor to cancer-related mortality.\textsuperscript{83} Thus there is a pressing need to improve treatment for this cancer to lower related morbidity and mortality.

\textsuperscript{79} Ibid.
\textsuperscript{80} Davis et al. (2011).
\textsuperscript{81} Tongdang (2008).
\textsuperscript{82} Kittipongpatana et al. (2011).
\textsuperscript{83} Arora et al. (2009).
ArtinM is a lectin derived from jackfruit that binds D-mannose and demonstrates high specificity for a trimannoside present in the core of N-glycans located on cell surfaces.\textsuperscript{84} Studies have shown that this lectin possesses many properties beneficial to health, such as the ability to speed up the healing of wounds and regeneration of epithelial tissue. It also acts on macrophages and dendritic cells—to establish in vivo Th1 immunity and confer protection against particular intracellular pathogens—as well as on neutrophils, to induce phagocytic and cell-killing activities.\textsuperscript{85} Such characteristics led to the trial of ArtinM as a potential anticancer agent against leukemia.

In one experiment, ArtinM was purified by affinity-chromatography from jackfruit seeds and tested against cells from a cell line called NB4 that serves as an appropriate model of acute promyelocytic leukemia (APL). Flow cytometry revealed that ArtinM was able to bind to over 95% of these leukemia cells, likely due to the modification of NB4’s surface glycans caused by malignant transformation. In addition, MTT assays indicated that NB4 cells were quite sensitive to ArtinM inhibition, with a 10 \( \mu \text{g/mL} \) concentration of the lectin reducing leukemia cell growth by half. NB4 cells cultured with ArtinM at this concentration for two days, at which point the cells were analyzed by flow cytometry. The lectin caused the pronounced surface exposition of phosphatidylserine, a phospholipid component generally located on the inside of the cell membrane. Hence, this analysis revealed signs of cellular apoptosis. ArtinM treatment also disrupted the mitochondrial transmembrane electrical potential in these leukemia cells.\textsuperscript{86}

ArtinM was also compared to all-trans-retinoic acid (ATRA), the main pharmacological component of APL therapy.\textsuperscript{87} Unlike drugs like ATRA, ArtinM was able to induce NB4 cell death without cell maturation. In addition, ArtinM treatment generated high levels of reactive oxygen species (ROS), which can lead to depolarization of the mitochondrial membrane translocation of apoptotic factors from the mitochondria to the nucleus. Therefore, the high ROS levels caused by ArtinM treatment can also induce leukemic cell death.\textsuperscript{88}

Therefore the jackfruit-derived lectin ArtinM has demonstrated the ability to mediate the death of human leukemia cells, a property that should be further explored in future studies as a potential mechanism by which to treat leukemia.

\textsuperscript{84} Misquith et al. (1994).
\textsuperscript{85} Carvalho et al. (2011).
\textsuperscript{86} Ibid.
\textsuperscript{87} Segalla et al. (2001).
\textsuperscript{88} Ibid.
Jute Applications

Wound Dressing

Jute has been used as a wound dressing since at least the 1800s, when the textile was used for medical applications much more frequently than today. Nevertheless, jute has reemerged as an effective wound dressing, in the form of a composite with polyvinyl alcohol (PVA). This hydrogel-based option is being developed in Bangladesh as a much more cost-effective option than many synthetic dressings currently available. The final product is intended to be even less expensive than similar hydrogel dressings based on a combination of agar, polyethylene glycol (PEG), and polyvinylpyrrolidone (PVP). In addition, other jute-based dressing options are being explored due to its mechanical properties. Its tenacity, defined as the force required to break the fiber, can be more than three times higher than cotton’s and six times greater than that of wool. Such mechanical properties make jute a fiber worth exploring for future wound dressing applications.

Arsenic Protection

Considered “one of the world’s biggest natural groundwater calamities,” groundwater arsenic contamination in India’s Ganga–Brahmaputra plains and Bangladesh’s Padma-Meghna plains has been a massive problem ever since the 1983 discovery of arsenic contamination in the region. By the year 2000,

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89 IAEA RCA (2003).
90 Hamlyn and Schmidt (1994).
91 Ghosh and Singh (2009).
approximately 60 million people in Bangladesh alone were drinking water contaminated with levels of arsenic above the United States EPA limit. Numerous harmful side effects—including cancers, circulatory system problems, nervous system damage, and skin problems—can result from consumption of unsafe levels of arsenic.

One study examined the effects of aqueous extract of *Corchorus olitorius* leaves (AECO) on arsenic-induced brain damage in rats. Five groups of six rats were given daily administrations, respectively, of: double distilled water for 15 days; arsenic (10 mg/kg) for 10 days; AECO (50 mg/kg) for 15 days followed by arsenic (10 mg/kg) for 10 days; AECO (100 mg/kg) for 15 days followed by arsenic (10 mg/kg) for 10 days; and quercetin (a weakly acidic flavonoid commonly found in nature) at 10 mg/kg for 15 days followed by arsenic (10 mg/kg) for 10 days. Their excised brains were then compared.

AECO treatment significantly decreased lipid peroxidation, likely through chemical mechanisms such as free radical quenching, electron transfer, or radical recombination. Probably owing to intrinsic antioxidant properties, AECO also helped combat the changes in levels of brain antioxidant enzymes—including superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST), glutathione peroxidase (GPx), and glutathione reductase (GR)—that arsenic exposure caused. These antioxidant enzymes are considered the first line of cellular defense against oxidative damage, so their restoration to normal levels is critical. Arsenic administration also negatively affected the levels of reduced glutathione (GSH) and oxidized glutathione (GSSG), cellular metabolites in the brain tissue that act as an additional line of defense. However, AECO treatment before the arsenic exposure helped rats prevent the toxin-induced alteration and maintain levels closer to normal, a result likely owing to the jute extract’s free radical scavenging abilities.

Figure 3.7 demonstrates the effect of AECO on two of the compounds previously discussed glutathione reductase and oxidized glutathione. In both cases, the

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92 Sambu and Wilson (2008).
93 Natural Resources Defense Council (2009).
94 Encyclopaedia Britannica (2012).
95 Das et al. (2009).
rats treated with AECO demonstrated substantially less damage than in the toxin control, and they were nearly at the same level as the standard quercetin. In addition, histological observations of brain tissue exposed to arsenic often revealed nuclear pyknosis, a degenerative state that involves chromatin condensation.

However, AECO administration prior to the arsenic treatment substantially lowered signs of pyknosis, left tissue architecture minimally changed, and yielded result comparable to rats treated with quercetin, the positive control. Therefore, despite the brain’s generally poor antioxidant defense, jute has demonstrated strong enough protective activity against arsenic-induced oxidative stress to encourage exploration of clinical applications in humans.

**Digesta Viscosity Elevation**

It is clear to most people that the contents of digesta—food being digested in the stomach—play a crucial role in human health. However, it is important to note that the viscosity of digesta is important as well. Studies have shown that nutrient diffusion in the laminar flow of the intestinal lumen is negatively dependent on digesta viscosity. Higher digesta viscosity also slows the glucose absorption rate in the intestinal lumen of humans and rats, thus lowering the increase in post-prandial blood glucose. This could provide notable health benefits to India’s growing diabetic population.

In the large intestine, increasing the digesta viscosity can decrease the fermentation rate by reducing the rate of encounter between bacteria and substrates. The increased digesta viscosity can also reduce diarrhea by decreasing succinic acid. This is significant given the severity of diarrhea as a major global health problem, particularly for children in the developing world. As of 2009, diarrhea was the second largest killer of children under 5 years of age, claiming approximately 1.5 million lives in that category every year (Fig. 3.8).

By supplying solid particles to the digesta, the addition of water-insoluble fibers like crystalline cellulose increases digesta viscosity and makes it harder for nutrients to move through the intestinal lumen and reach the absorptive surface. Insoluble fibers for such applications can be fabricated from the dried leaves of tossa jute.

96 Das et al. (2009).
97 Antoon and Kirsch (1982).
98 Takahashi et al. (2005).
99 Takahashi (2011).
100 UNICEF/WHO (2009).
101 Takahashi and Sakata (2005).
When compared to shiitake mushroom (*Lentinus edodes*), a compositionally similar source of insoluble fiber, tossa jute induced a higher coefficient of viscosity at any given shear rate. Tossa jute also demonstrated substantially higher swelling, water-holding, oil-holding, and cation exchange capacities in comparison to shiitake. This is especially noteworthy because insoluble fibers with higher swelling or water-holding capacities have increased digesta viscosities due to reduced digesta free water content. In rats that were administered tossa jute fibers, the gastric, small intestinal, and caecal digesta viscosities were nine, three, and one times (respectively) greater than those of rats that received crystalline cellulose fibers. Hence, insoluble jute fibers have demonstrated their effectiveness in raising digestive viscosity and altering digestion and nutritional absorption as a result.102

### Rice Applications

#### Protein Production

Transgenic rice seeds can be used to produce functional human serum albumin (HSA) protein. HSA serves as a monomeric carrier protein for steroids, thyroid hormones, and fatty acids while also helping to stabilize extracellular fluid volume.103 Its medical applications range from liver cirrhosis treatment to a cell culture medium for vaccine production to a treatment for severe burns.104, 105 New applications of HSA being explored include carrier of oxygen, fusion of peptides,  

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102 Takahashi et al. (2009).
103 Peters (1995).
104 Alexander et al. (1979).
105 Hastings and Wolf (1992).
and nanodelivery of drugs.\textsuperscript{106} HSA is in high demand worldwide—at over 500 tons per year—but there are several major problems facing its use. Since commercial HSA production is currently based on collected human plasma, the limited supply has led to the production of unsafe, fake albumin.\textsuperscript{107} In addition, this method of acquiring plasma-derived HSA (pHSA) carries with it the risk of spreading infectious, blood-derived pathogens such as HIV or hepatitis.\textsuperscript{108} Therefore, researchers have been seeking alternate ways to produce safe recombinant HSA (rHSA).

One method to do so involves rice seeds, which are an effective means to produce recombinant proteins due to their ability to generate high levels of stable protein and be controlled well on a production scale. One study used a strong endosperm-specific promoter along with its signal peptide to target rHSA into protein storage vacuoles and enabled transcription of the HSA gene with by using rice-preferred gene codons. This led to \textit{Oryza sativa} recombinant HSA (OsrHSA) expression levels of up to 10.58\% in the endosperm of the transgenic plants. The phenotype and crystal structures of OsrHSA are displayed in Fig. 3.9.

This OsrHSA was found to be equivalent to pHSA with regards to biochemical properties, functions, immunogenicity, and physical structure. With respect to structure and properties, OsrHSA and pHSA had the same amino acid sequence, melting point, molecular mass, and N- and C-terminus. Circular dichroism and spectroscopic analysis also revealed that OsrHSA and pHSA have identical secondary and tertiary structures as well as the same general conformations. In terms of function, OsrHSA and pHSA demonstrated similar ligand binding affinities at site-specific drug markers as well as comparable cell growth promotion across three common cell lines. The two also showed similar efficacy in the treatment of liver cirrhosis, as evaluated in a rat liver ascite model.

Immunoprecipitation experiments and ELISA tests indicate that OsrHSA’s immunogenicity in vitro is similar to that of pHSA, and analysis of the antibody titer in rabbit serum after OsrHSA or pHSA immunization indicate that the two also have the same immunogenicity in vivo. The study also demonstrated that producing HSA from transgenic rice seeds was quite inexpensive, particularly compared to current methods. Therefore, OsrHSA is a suitable alternative to pHSA that can be produced from rice seeds on a large scale in a cost-effective manner.\textsuperscript{109}

Studies have also shown that it is possible to use rice to produce human lactoferrin (hLF), a multifunctional milk protein involved in biological processes such as bone growth promotion, immune system modulation, iron absorption, and antimicrobial activity. Other transgenic organisms—including cows, fungi, potatoes, and tobacco—have successfully expressed hLF, but rice possesses several

\textsuperscript{106} Tsuchida et al. (2009).
\textsuperscript{107} Xinhua News Agency (2007).
\textsuperscript{108} Erstad (1996).
\textsuperscript{109} He (2011).
advantages over these other vehicles. The rice system is well-suited to low-cost mass production of hLF and yields expression 25–40 times higher than any other plant system while having the lowest potential (of commonly consumed grains) for causing human allergies. Rice can also stably store expressed foreign proteins in their grains for years. One study showed that 1 hectare of rice could yield up to 40 kg of hLF. In addition, the hLF does not have to be purified from the rice, further simplifying the process to prepare the rice for consumption.

Although this method poses a risk of possible contamination of non-transgenic rice, researchers developed a built-in strategy to combat this threat. They tagged the gene of interest with an RNA interference cassette that would suppress the expression of an enzyme that detoxifies the herbicide bentazon, so hLF could easily be selectively killed using bentazon. Thus, biologically active hLF that is functionally similar to the native human milk protein can also be successfully produced from transgenic rice seeds.

Multifunctional Excipient

Rice germ oil (RGO) is made up of triglycerides and comes from the *Oryza sativa* family. This edible oil is a great source of the antioxidant gamma-oryzanol, which has medical applications ranging from plasma lipid level maintenance to platelet aggregation prevention. Studies have shown that RGO can serve as a suitable multifunctional excipient to carry the active components of a particular medication.

For example, take the case of tacrolimus (TAC), an antibiotic with strong immunosuppressive qualities often administered following an organ transplant to prevent organ rejection. Owing to first-pass metabolism, inter-subject variability, and poor solubility, TAC has very low, variable bioavailability. However, a novel drug delivery system called SMEDDS—self-microemulsifying drug delivery system—has the potential to change this. SMEDDS involves an isotropic combination of drug, oil, surfactant, and co-surfactant that will spontaneously microemulsify upon exposure to gastrointestinal fluid. SMEDDS has some drawbacks, including its restricted solubilization efficiency and its use of antioxidant to inhibit auto-oxidative oil deterioration. Although there are current ways

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110 Lin et al. (2010).
111 Huang (2004).
112 Lin et al. (2010).
113 Kim et al. (2002).
114 Garcia et al. (2009).
115 Pawar and Vavia (2012).
116 Constantinides (1995).
117 Zhang et al. (2004).
to combat these limitations, studies have shown that such methods might involve mutagenic and carcinogenic properties. But using multifunctional excipients with high-solubilization efficiency and inherent antioxidant properties could circumvent this problem.

Research has shown that RGO is precisely such a multifunctional excipient, one that can diminish bioavailability and solubility issues that TAC has. In vitro studies showed that a SMEDDS formulation using RGO resulted in the full release of TAC within thirty minutes, while plain TAC and a TAC marketed capsule demonstrated less than 5 and 50% drug release, respectively, in the same timeframe. RGO’s natural antioxidant characteristics also prevented auto-oxidative deterioration in TAC-SMEDDS, and the formulation was proven to be stable (over a 3-month period) and compatible with hard gelatin capsules. In addition, TAC-SMEDDS demonstrated a relative bioavailability that was 1.5 times greater than that of the TAC marketed capsule and 3.5 greater than the plain TAC. Maximum concentration displayed a similar effect, with TAC-SMEDDS having concentrations that were 1.69 times higher than the TAC marketed capsule and 8.14 times higher than the plain TAC. Therefore, rice germ oil has demonstrated its promise as a multifunctional excipient for a novel drug delivery system such as that employed in TAC-SMEDDS.

**Porous Scaffolds**

Good scaffolds for bone tissue engineering should be able to deliver cells while possessing good bioactivity, biodegradability, osteoconductivity, and mechanical properties. They should also have suitable porosity with larger pores to allow tissue ingrowth and new tissue vascularization and smaller pores to encourage protein adhesion as well as cell adhesion and proliferation. Bioactive glasses and glass–ceramics have become an important material for bone regeneration, since they possess excellent bioactivity, controllable biodegradability, osteoconductivity, and the ability to deliver cells. They also have demonstrated the ability to bond...
to bone in vivo by forming a hydroxyapatite surface layer. However, porosity often poses a challenge.\textsuperscript{120}

Rice husk, an abundant material typically regarded as waste, could help solve this problem. In the 2006–2007 year alone, 80 million tons of rice husk were produced, meaning that every 5 tons of rice production yielded approximately 1 ton of rice husk. Rice husk is often used for bedding or burned to generate energy, the latter of which adds to environmental pollution.\textsuperscript{121} But scientists have discovered a new biomedical application for this waste material. In bioactive glass and glass–ceramic scaffolds, powdered rice husk can be used as an additive to form pores that will contribute to bone growth.

One study mixed 45S5 Bioglass\textsuperscript{®}—a bioactive glass–ceramic derivative of high-purity SiO\textsubscript{2}, Na\textsubscript{2}CO\textsubscript{3}, CaCO\textsubscript{3} and P\textsubscript{2}O\textsubscript{5} which is currently used for middle ear and dental implants—with rice husks that had particle sizes below 600 \textmu m to create scaffolds. With blends that contained 70–80 wt % rice husk, scaffolds displayed both macropores (at least 420 \textmu m in length and 100 \textmu m in breadth) and mesopores (between 25 and 80 \textmu m in size).\textsuperscript{122} Micropores in the macropore surface increased surface area substantially, thereby facilitating protein adsorption as well as ion-exchange and bone-like apatite surface formation while providing a good microenvironment for cell differentiation and bone matrix deposition.\textsuperscript{123}

Figure 3.10 shows the change in surface morphology and increase in surface area after a 75 wt % rice husk blend scaffold is sintered and submerged in simulated body fluid (SBF) for varying amounts of time.

These scaffolds achieved compressive strength in the range of trabecular bone and the scaffolds with higher proportions of rice husk also demonstrated greater mechanical properties.\textsuperscript{124} Therefore, rice husk enabled the creation of a porous, bioactive glass–ceramic scaffold for bone regeneration that can provide temporary mechanical support before biodegrading at an appropriate time, and do so in an environmentally friendly and cost-effective manner.

**Sutures**

Scientists have developed a rice-starch carbon nanocomposite biomaterial that serves as a suturing material. Normally, rice starch can be easily formed into polymer films, but the hydrogen bonds between hydroxyl groups in the matrix of

\textsuperscript{120} Wu et al. (2009).
\textsuperscript{121} Luduena et al. (2011).
\textsuperscript{122} Wu et al. (2009).
\textsuperscript{123} Kawai et al. (1997).
\textsuperscript{124} Wu et al. (2009).
these films are quite weak. As a result, these natural polymer-based films generally have poor mechanical qualities, particularly with respect to high percentage elongation, tensile strength, and flexural strength. Therefore, it is useful to reinforce rice starch-based films and filaments with other materials to form a more stable composite.

In one study, researchers mixed rice starch in solution with gelatin, sodium carboxymethylcellulose, polyvinyl alcohol, and glycerol before adding carbon powder—derived from coconut shell charcoal—to create a homogeneous mixture. This solution was then dried and formed into stable sutures. These sutures possess a high water resistance and high mechanical strength while also being biocompatible and bioabsorbable, which makes them good candidates for human body suturing applications. The tremendous improvement in mechanical properties was demonstrated by the fact that a 10 wt % addition of carbon nanopowders to the rice starch polymer film increased the film’s elastic modulus by approximately 140 % and raised the tensile strength by about 1200 %. In addition, these rice starch composite sutures are low-cost, environmentally friendly, and relatively simple to manufacture. Thus, they offer many benefits and warrant further exploration, particularly for use in India.

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125 Li et al. (2008).
126 Punyanitya (2010).
127 Ibid.
Silk Applications

Corneal Grafts

Microbial keratitis is an infection that can progressively damage the corneal epithelium and stroma to the point of scarring, perforation, or blindness. In fact, corneal diseases such as infective keratitis are the second largest cause of vision loss and blindness. This is a particularly large problem in India, where the incidence of corneal infections has been reported at 10 times that of the United States.\(^{128}\) Corneal blindness is a substantial problem in Indian public health, with many people sustaining corneal injuries from infections, childhood fevers, or chemical injuries that lead to vision loss.\(^{129}\) Such damage often requires a corneal graft to restore vision. As of 2005, corneal grafts were the most common type of tissue transplant in the US, where nearly 10 million people were suffering from vision loss as a result of corneal blindness.\(^{130}\) However, within 5 years of implantation, about 1 in 4 patient immune systems rejects the corneal graft.\(^{131}\)

Silk proteins have significant potential for such corneal tissue engineering applications. In order to develop a new biomaterial option with lower rejection rates, scientists have begun to study silk fibroin, a structural protein from the *Bombyx mori* silkworm cocoon. This protein exhibits controllable degradation rates, non-immunogenic responses in implantation, and robust mechanical properties, making it a suitable candidate for corneal tissue replacement.\(^{132}\) Silk fibroin is also one of the strongest, toughest natural fibers known to man.\(^{133}\) Fibroin can be used to create transparent, patterned biomaterials that allow sight and provide a surface to help direct cellular function and matrix deposition.\(^ {134, 135}\) Unlike materials such as synthetic polyglycolic acid or natural collagen, the biodegradation rates of silk fibroin can be manipulated to allow extra time for native tissue to remodel.\(^{136}\) In addition, biopolymers like collagen and fibrin involve complex processing steps and are difficult to transform into mechanically stable structures, whereas silk is much easier to manipulate and it forms a very robust structure.

The ability to create patterned cell-guiding surfaces as well as porous structures to assist with nutrient diffusion and inter-layer cell interaction further increases the attractiveness of silk-based biomaterials for corneal tissue engineering. The

\(^{128}\) Bharathi et. al. (2009).
\(^{129}\) Dandona et al. (1998).
\(^{130}\) Eye Bank Association of America (2005).
\(^{131}\) Georgea and Larkin (2004).
\(^{132}\) Lawrence et al. (2008).
\(^{133}\) Altman et al. (2003).
\(^{134}\) Jin et al. (2005).
\(^{135}\) Chirila et al. (2008).
\(^{136}\) Hu et al. (2005).
patterned films—such as the one pictured in Fig. 3.11—enabled enhanced cell alignment and synthesis of the extracellular matrix, both of which help the biomaterial mimic the native cornea’s layered and aligned structures.

In particular, a rabbit corneal cell line expressing green fluorescent protein (GFP-rCF) and human corneal fibroblast (hCF) cell line successfully adhered to, proliferated through, and produced native matrix upon the optically transparent, self-standing silk film substrates. The patterned film helped direct cell and actin filament alignment, and the hCF remained viable and fully proliferated the silk construct within ten days. The silk film structures also exhibited potential to be used as scaffolding in tissue engineering applications, due to the initial native matrix that was produced. Thus, studies have shown the viability of 3D fibroin-based structures to be used as corneal grafts and demonstrated the ability for such silk film constructs to serve as scaffolding for other tissue engineering purposes.137

**Optical Devices**

Today, there are no available optical devices that are mechanically robust while also being fully biodegradable and biocompatible, so many potential medical applications are restricted to retrievable devices. However, silk could change this. Scientists have successfully constructed silk biomaterials with high optical clarity and readout capacity that can achieve complex diffractive structures including lenses and predefined one-dimensional and two-dimensional light patterns. They have created free-standing films between 10 and 100 μm in thickness with transmission across the visible spectrum consistently registering above 90%. Measured diffraction efficiencies of the silk structure gratings compared favorably to the transmissive glass gratings often used today.138

In addition, the unique processing technique required to create these optical silk structures means that they can be designed to more easily incorporate biologically active elements in a manner that poses less of a risk (in terms of potential toxic chemical leaching) to biomedical applications than current systems, which often involve methanol. Research showed that a number of biological substances—including physiologically relevant proteins, enzymes, and small organic pH indicators—could be successfully embedded in the silk films. The introduction of such dopants did not appear to have a significant effect on the film structure, with thickness and refractive indices remaining quite constant.

To test for substrate biocompatibility, red blood cells were included in the silk grating. Hemoglobin, the oxygen-carrying protein inside the red blood cells, was able to maintain activity within the silk structure’s matrix, as demonstrated by optical transmission experiments. To study the inclusion of enzymes in the silk

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137 Lawrence et al. (2008).
138 Lawrence et al. (2009).
films, horseradish peroxidase (HRP) was added to the silk solution along with an organic monomer called TMB that changes color in the presence of HRP. Measurements showed that HRP was still active within the silk structure’s matrix up to 45 days after initial preparation of the grating. In order to evaluate the silk structure’s compatibility with small molecules, Phenol Red, an organic pH indicator, was incorporated. The resulting diffractive optic structures were able to retain both the indicator’s functionality and the optical function of the diffraction grating.\footnote{Lawrence et al. (2009).}

The silk structure’s biocompatible nature and ability to completely biodegrade is also critical. These characteristics enable the structure’s use in devices that could unobtrusively enter and monitor an environment such as a human body. The silk’s degradation time could be manipulated such that the device could be used for remote sensing and detection systems but would safely degrade in the environment at an appropriate time, thereby sparing a patient an invasive surgery or other extraction process. Such devices could include everything from an internal glucose meter to hydrogen peroxide detectors. Therefore, silk-based optical devices hold a tremendous amount of promise for future biomedical sensor and detection systems that can be both mechanically durable and fully biodegradable.\footnote{Lawrence et al. (2009).}

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\textbf{Fig. 3.12} Scanning electron microscope images of a PN200 Spidrex\textsuperscript{®} Silk conduit. Honeycomb-like conduit outer sheath with luminal silk fibers (\textit{scale bar} = 100 \(\mu\text{m}\)). Transverse faces of luminal silk fibers at higher magnification (\textit{scale bar} = 10 \(\mu\text{m}\)). (Huang et al. 2012)
Another potential application of silk is the creation of artificial conduits for nerve repair. Nearly 3% of all trauma patients suffer from peripheral nerve injury and regeneration often does not go smoothly. Although the introduction of autographs helped bridge longer-distance nerve grafts without placing the nerve stumps in tension—a problem faced for many years—it still has a range of shortcomings, such as scar tissue invasion, incomplete functional recovery, lack of donor nerves, morbidity from secondary injury, and limited length. Artificial conduits—which help guide regenerating axons from the proximal to the distal segment—are a promising way to alleviate some of these problems, as they eliminate the risk of secondary injury, reduce scar tissue infiltration, and possess modifiable length, diameter, and permeability. But researchers have been struggling to construct the ideal conduit, one that is environmentally compatible and can be easily created in the desired size, that promotes axonal regeneration with a supportive luminal scaffold, and that protects regenerating axons from scar tissue infiltration. The luminal scaffold issue has proven especially tricky, particularly since there are no conduits with luminal scaffolds in clinical use today.

Recently produced silk-based conduits might help solve this problem. These conduits—which consist of a tube of regenerated Bombyx mori silk protein with a luminal scaffold of spider silk-like biomaterial filaments—were shown to promote neurite growth. Figure 3.12 shows close up images of such a silk-based conduit. When compared to a non-silk-based nerve guide of poly-3 hydroxybutyrate (PHB) tube, the silk-based conduit performed better in the spinal ganglia of male rats. Approximately 1 month after surgery, axonal labeling mid-conduit was 62% of the autologous graft, as opposed to 58% with the PHB conduit. A study using polytetrafluoroethylene (PTFE), silicone, and nerve autograft to bridge a 10 mm gap in a rabbit sciatic nerve showed an average axon count of 48% in the distal nerve after 13–15 weeks for the PTFE group compared to the nerve graft. Silk conduits, however resulted in 81% of the number of myelinated axons at 12 weeks, compared to autologous controls.

With respect to biodegradability, three of the five types of conduits presently FDA-approved for clinical nerve repair are either non-biodegradable or degrade...
in as little as 8 weeks, which might be too soon to support axonal growth across long gaps. On the other hand, the silk-based conduits are predicted to be resorbed within 1 year, a timeframe more suited to longer distance repairs. In addition, silk conduits did not trigger a major inflammatory tissue response, which could be a significant advantage over some synthetic nerve guidance channels that elicited a chronic inflammatory response.\footnote{Huang et al. (2012).}

Therefore, silk-based conduits could prove to be an excellent candidate for clinical nerve regenerative applications in the future. This is particularly important given that an international panel of nearly fifty experts recently ranked nerve regeneration technologies as the 9th most important regenerative medicine application for improving health in developing countries.\footnote{Greenwood et al. (2006).}

\section*{Bone Regeneration}

Silk-based scaffolds with a similar lamellar structure as bone have been designed that are useful for tissue engineering and bone regeneration.\footnote{Oliveira et al. (2012).} In particular, clay montmorillonite and sodium silicate on a silk fibroin organic scaffold offers a mechanically stable scaffold for bone growth.\footnote{Mieszawska et al. (2011).}

For large bone defects, autologous bone transplants can be used to regenerate the bone, but this method is usually dismissed in favor of biomaterial usage in order to avoid the additional pain, conformal needs at the repair site, longer rehabilitation times, and second site morbidity associated with such transplants.\footnote{Langer and Vacanti (1993).} Numerous biomaterials have therefore been studied for this purpose, and collagens have emerged as a suitable biomaterial. Collagens are a natural polymer source that reflect the major source of proteins in the extracellular matrix of bone and interact well with tissue, but they do not possess long-term mechanical stability or integrity.\footnote{Riesle et al. (1998).} Therefore, silk has emerged as a better possible alternative. Silk possesses extraordinary mechanical properties: for example, silk fibers can absorb approximately the same amount of energy before failure as Kevlar.\footnote{Sofia et al. (2001).} In addition, purified silk is highly compatible and can demonstrate very slow degradation times.\footnote{Meinel et al. (2005a).} Hence, researchers tested silk fibroin-based scaffolds seeded with human
mesenchymal stem cells (hMSC) to promote sustainable bone growth to test their effectiveness in bone regeneration.  

These scaffolds created a protein matrix that could slowly degrade and allow for some degree of control over hydroxyapatite bone mineral deposition over time. In bioreactor studies, this enabled the creation of a bone matrix similar to that of spongy bone. According to biochemical assays, gene expression analysis, and X-ray diffractometry, the organic and inorganic components of bone tissues engineered in this manner were quite similar to those of bone. These silk-based, tissue-engineered implants were grown in bioreactors for 5 weeks before introduction into 7-week old mice with circular defects (4 mm in diameter) in their skulls. Within 5 weeks of implantation, the tissue-engineered bone implants demonstrated advanced bone formation. Levels of osteopontin (a sialoprotein that can bind calcium and hydroxyapatite and facilitate cell adherence) and osteocalcin (a secretion of osteoblasts, which are largely responsible for proper bone formation) were also quite high. Thus, in conjunction with engineered bone, silk-based implants have demonstrated sizable promise for effective osteogenesis in a mechanically stable manner.  

In addition, sonication-induced silk hydrogels have been created as injectable bone replacements. Studies have evaluated sonication-induced silk hydrogels encapsulating vascular endothelial growth factor (VEGF165) and bone morphogenic protein-2 (BMP-2)—two important regulators of angiogenesis and osteogenesis during bone regeneration—for slow release. A study performed on 24 male rabbits with irregularly shaped sinuses showed that these silk-based hydrogels promoted good bone formation and had advantages over current methods, including good plasticity, minimal invasion, simple preparation, and short utility at operation time. In addition, this method was quite simple to use, since its injectable form enabled easier administration given smaller bone windows. The release of VEGF165 and BMP-2, which were used to quantify growth factor release from silk gels, demonstrated an impressive ability to resist “bursts” and release the factors according to sustained kinetics over the course of at least 4 weeks. Therefore, silk hydrogels have exhibited potential for use as a minimally invasive means to deliver multiple growth factors via injection to specific locations and assist with bone regeneration in irregular cavities.  

**Drug Delivery**

Beads, hydrogels, and nanoparticles from silk fibroin matrices have also been used for drug delivery. For example, silk fibroin and polyacrylamide semi

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159 Meinel et al. (2005b).
160 Meinel et al. (2005a).
161 Zhang et al. (2011).
162 Bhardwaj et al. (2011).
Interpenetrating network (semi-IPN) hydrogels have been synthesized to serve as a matrix for sustained drug release with improved mechanical strength and greater drug immobilization capabilities than plain hydrogels. This type of hydrogel was easily fabricated and manipulated with respect to factors such as degradation, mechanical strength, porosity, and swelling. When drug release tested using two model compounds—trypan blue dye and fluorescence isothiocyanate labeled inulin (FITC-Inulin)—the hydrogels demonstrated good release kinetics, though factors such as molecular weight, water solubility, and polymer ratios all influenced the outcomes.163

Silk fibroin beads created from scaffolds embedding calcium drug delivery demonstrated the success of silk in dual drug delivery applications. It was able to control and release two model compounds of different molecular weights—bovine serum albumin (BSA) and FITC-Inulin—independently and in a sustained manner. The silk in these systems also helped slow down the drug release to enable sustained delivery and avoid rapid initial bursts. Thus, these silk-based beads have successfully demonstrated a way to deliver multiple active drug molecules from a single delivery system in a regulated manner, a development that could be very important to improvements in modern drug delivery systems.164

Spherical silk fibroin nanoparticles for drug delivery purposes have also been formulated from both mulberry silkworms (Bombyx mori) and non-mulberry silkworms (Antheraea mylitta). Confocal laser scanning microscopy with the FITC-tagged nanoparticles demonstrated their cellular uptake in murine squamous cell carcinoma cells in less than 1 h. Most of these nanoparticles were endocytosed and found in the cytoplasm near the nuclear membrane, where they were able to remain stable. The non-mulberry fibroin nanoparticles were also used to study vascular endothelial growth factor (VEGF) release. VEGF was quite easily loaded into the nanoparticles and the silk allowed for a more controlled, sustained release in comparison to a control system without silk nanoparticles. This demonstrated the nanoparticles’ potential for future use in therapeutic drug delivery systems.165

Non-mulberry Antheraea mylitta silk sericin protein has also been used with amphiphilic poloxamers to create self-assembled micellar nanoparticles for targeted delivery of both hydrophilic and hydrophobic drugs. FITC-inulin was used to study hydrophilic drug carrying abilities. Nanoparticles successfully encapsulated the drug and demonstrated enhanced stability after 10 days of incubation. To observe their behavior as a hydrophobic drug carrier, the nanoparticles were loaded with paclitaxel, an extremely effective anticancer agent. Treatment of breast cancer MCF-7 cells with the paclitaxel-loaded nanoparticles substantially reduced cell growth and increased cell death. Although drug loading was not as high as for free paclitaxel drug delivery, these silk-based nanoparticles may still be preferable because free paclitaxel is less soluble and has a high affinity to other

163 Mandal et al. (2009).
164 Mandal and Kundu (2009a).
165 Kundu et al. (2010).
plasma proteins. Therefore, even at lower concentrations, the drug-loaded sericin nanoparticles can directly enter cells and display functionality, lowering the risk of side effects related to high drug dosages.\textsuperscript{166}

**Cartilage and Ligament Repair**

Given the frequency of injuries and injury-related death due to physical trauma such as traffic accidents, effective ways to generate and repair cartilage in developing countries like India are becoming increasingly important. Pure silk and blended silk fibroin scaffolds have both demonstrated promise for in vitro tissue engineering of cartilage. Several studies have used bovine chondrocytes (the cells that comprise cartilage) to examine properties such as biomechanical strength, cell viability, and proliferation. These studies have revealed the importance of initial cell seeding with mesenchymal stem cells, particularly with respect to density, since the seeding affects extracellular matrix production and biomechanical properties.\textsuperscript{167}

Studies have also demonstrated the use of silk scaffolds for ligament tissue engineering. One such study replaced the silk fiber’s sericin with gelatin using a cross-linking agent in order to mimic the silk fiber’s natural structure and maintain its structural properties like strength while removing the risk of an adverse immune response that sericin could trigger. These scaffolds demonstrated superior

\textsuperscript{166} Mandal and Kundu (2009b).

\textsuperscript{167} IAEA RCA (2003).
mechanical properties and environmental stability when compared with scaffolds made of poly-L-lactide (PLLA) or polylactic-co-glycolic acid (PLGA).\textsuperscript{168}

**Multi-Functional Stents**

Cardiovascular disease has become an increasingly significant problem in India, as it is now the leading cause of death. It is also a substantial source of morbidity, with 9.2 million potentially productive years of life lost in 2000 due to cardiovascular conditions and the number of hypertensive individuals expected to surge to 214 million in 2025.\textsuperscript{169} The severity of cardiovascular disease in India has also led to an increase in cardiovascular surgical procedures, including the implanting of stents. In particular, drug-eluting stents have become increasingly common. India has become one of the fastest-growing markets for drug-eluting stents in the world, with over 150,000 such stents implanted in the country every year.\textsuperscript{170}

Despite the benefits brought about by stent implantations, the deep vascular injury and endothelial cell damage caused by the procedure in conjunction with long-term exposure to the foreign metallic device often leads to excess vascular smooth muscle cell (SMC) proliferation, thrombosis (formation of a blood clot in a blood vessel or occlusion of the stent),\textsuperscript{171} and restenosis (decreased lumen diameter after percutaneous coronary intervention)\textsuperscript{172, 173} However, scientists have successfully developed a silk-coated stent capable of releasing drugs over time to alleviate these conditions. Multiple coatings of *Bombyx mori* silk fibroin were loaded with heparin—a naturally occurring anticoagulant also used to coat catheters, metallic stents, and other devices\textsuperscript{174}—as well as the chemotherapy drug paclitaxel and the anti-platelet agent clopidogrel to examine their anti-coagulative properties as well as their anti-proliferative effects on smooth muscle cells and endothelial cells. These drug-eluting devices were able to regulate adhesion, viability, and growth of human aortic endothelial cells as well as human coronary artery SMCs in vitro. They also did not compromise on their “primary” function, successfully expanding and holding open the arteries just like regular stents.\textsuperscript{175}

In addition, in vivo studies of a porcine aorta revealed that the silk coatings maintained integrity after implantation and were able to successfully reduce

\textsuperscript{168} Liu et al. (2007).
\textsuperscript{169} Reddy (2007).
\textsuperscript{170} BioSpectrum Bureau (2011).
\textsuperscript{171} Mollichelli et al. (2010).
\textsuperscript{172} Dangas et al. (2010).
\textsuperscript{173} Wang et al. (2008).
\textsuperscript{174} Hanson (1998).
\textsuperscript{175} Wang et al. (2008).
platelet adhesion to the coatings, due to their drug contents. This result is visible in Fig. 3.13, where less platelet adhesion has occurred on the silk-coated stents with heparin.

Hence, these multifunctional stents offer a promising way to efficiently treat cardiovascular disease, and such combination devices could likely be applied to other conditions as well.

**Soy Applications**

**Bone Regeneration**

Researchers have created strong, cost-effective composites by combining biodegradable soy-protein polymer and specific bioabsorbable polyphosphate reinforcing fillers. Such biocomposites are nontoxic and bioabsorbable, making them well-suited to medical device applications. These composites are more water-resistant than natural polymers, so they are better able to maintain necessary stiffness in the moist environments present throughout the body.

More specifically, soybean-based biomaterials have demonstrated tremendous potential for bone regeneration purposes. When a bone defect achieves a critical size—as in certain traumatic events or surgical procedures where pathological conditions require bone removal—bone regeneration no longer regenerates spontaneously. Hence there is a need for bone fillers to support bone formation. Human or animal bone grafts (mineralized or non-mineralized) are currently the best option for most of these cases, but such grafts are often in short supply and can increase morbidity and risk of transmittable disease. There are also several categories of synthetic bone fillers which have been shown to support proliferation of bone-producing cells or completely degrade into carbon dioxide and water. However, these two have shortcomings, from brittle mechanical properties to triggering unwanted inflammatory responses. Soybean-based materials offer a simple, inexpensive solution to these problems, as they may exert bioactivity on cells (enhancing tissue regeneration) and they could self-counter any immunogenic response.

One manner in which this has been achieved is by thermosetting defatted soybean curd. The resulting biomaterial is very ductile, enabling effective adaptation to the implantation site and providing the damaged tissue with a biocompatible, biodegradable scaffold. In addition, this soybean-based biomaterial has demonstrated the potential to reduce the chronic inflammatory response induced by macrophages while also promoting bone regeneration by stimulating bone cells. The soybean biomaterial’s release of particular isoflavones decreased the activity

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176 Ibid.
177 Otaigbe (1998).
178 Santin (2007).
of osteoclasts (the cells responsible for bone resorption) and macrophages, thereby speeding up the healing process. Data also indicates that, when combined with induced collagen synthesis, this soybean-based bone filler is able to set off most of the cellular and biochemical events necessary for synthesizing new mineralized tissue.\textsuperscript{179} Therefore, this soybean-based biomaterial may prove to be a relatively inexpensive and easily manufactured bone filler with improved biological and physicochemical characteristics for clinical applications.

Other formulations of soybean-based biomaterials have also shown promise as bone fillers.\textsuperscript{180} For example, two different soybean-based filler formulations were compared in vivo to a polylactic acid/polyglycolic acid (PLA/PGA) copolymer used in bone grafts as a bone regenerating material for oral surgery or a space filler for tissue regeneration.\textsuperscript{181} The first was a 50:50 (by weight) blend of 212–300 \( \mu \)m tofu granules and hydrogel derived from defatted commercial soy flour. The second was a preparation in the proportion of 300 mg soybean-based hydrogel powder with 150 mg soybean granules (of size 212–300 \( \mu \)m) and 100 \( \mu \)m 0.1 M CaCl\(_2\) solution. These two soybean-based fillers as well as the commercial PLA/PGA filler were inserted into defects 6 mm in diameter and 10 mm in length in male rabbit femurs.

The soybean-based fillers clearly promoted bone repair and even demonstrated some advantages over the PLA/PGA filler. For example, 8 weeks after implantation, the soybean-based bone fillers promoted a higher level of bone in-growth than the PLA/PGA filler in two-thirds of cases. Also, bone in-growth in the rabbits treated with soybean-based filler progressively improved over the 24 week period of study, while the rabbits treated with the commercial filler displayed clear signs of bone resorption by the eighth week.\textsuperscript{182} This resorption is likely due to an inflammatory response triggered by small pieces of degraded PLA/PGA filler, a problem that soybean-based fillers did not encounter.\textsuperscript{183} However, the soybean-based biomaterials also encountered some problems. A few rabbits, for instance, demonstrated excessively packed granules. Such models did not permit sufficient bone infiltration and could potentially lead to fibrosis. Nevertheless, this spacing problem is one that could likely be optimized through formula adjustment in order to encourage osteoid infiltration and a progressively mineralizing front. Hence, these soybean-based fillers have demonstrated substantial bone regeneration abilities, likely by using the biomaterial as a scaffold for osteoblasts and inducing cell differentiation. In the future, they could serve as desirable alternatives to methods like autologous bone grafts or PLA/PGA hydrogels, particularly given their ductility and lack of a brittle nature or excessively loose consistency.\textsuperscript{184}

\textsuperscript{179} Ibid.
\textsuperscript{180} Giavaresi et al. (2009).
\textsuperscript{181} Rimondini et al. (2005), Zaffe et al. (2005).
\textsuperscript{182} Giavaresi et al. (2009).
\textsuperscript{183} Hedberg et al. (2005).
\textsuperscript{184} Giavaresi et al. (2009).
Soy has also demonstrated potential applications in inflammatory disorder treatment. With disorders such as inflammatory bowel disease (IBD), the gastrointestinal tract can be chronically inflamed, leading to such problems as weight loss, gastrointestinal permeability, and digestive tract distress.\textsuperscript{185, 186} While there are treatments available for IBD that use drugs and immunosuppressants to target inflammatory molecules, they often have high costs and negative side effects, in addition to occasional low efficacy.\textsuperscript{187} Hence, there is currently interest in creating new therapies that are not cytotoxic and can be easily absorbed and disseminated to the site of inflammation while remaining highly effective. Various soy proteins and phytochemicals—including isoflavones, saponins, trypsin inhibitors, and lunasin—have been examined and found to reduce both inflammation and the expression of inflammatory genes in vitro and in vivo.\textsuperscript{188}

One study examined the effects of soy-derived di- and tri-peptides on pigs, whose gastrointestinal tracts are morphologically and physiologically similar to those of humans.\textsuperscript{189} The pigs were treated with dextran sodium sulfate (DSS) to induce intestinal inflammation and infused with the peptides via catheter. Although treatment with the soy peptides did not substantially affect symptomatic and growth performance factors linked with inflammation, they did help lessen macroscopic indicators of colonic inflammation and intestinal permeability. Peptides exhibited a protective effect in pig colons, helping them maintain an intact epithelium despite the tissue-erosive effect of DSS. Peptide-treated pigs also demonstrated lower colonic crypt depth than those who only received the DSS and similar muscle thickness to control pigs that received neither DSS nor peptides, indicating that the peptides prohibited their intestines from undergoing the typical damage-and-recover cycle of DSS-treated pigs. In addition, soy peptides substantially lowered TNF protein and expression levels. The suppression of TNF has

\begin{figure}
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\includegraphics[width=\textwidth]{structures.png}
\caption{Structures of the three model drugs. Xu and Yang (2009)}
\end{figure}
demonstrated promise for IBD treatment, particularly since intestinal inflammation usually triggers an increase in the expression of TNF and other inflammatory mediators which help release other proinflammatory cytokines, thus drawing out the immune response. The peptides’ lowering of levels of the inflammatory mediator IFNG similarly indicates reduced colonic inflammation. Soy-peptide treatment also lowered the levels of cells often associated with Crohn’s disease, another common form of IBD.190

Thus, soy peptides were able to successfully suppress the expression of inflammatory mediators, as shown by the inhibitory effects on histological measurements and gut permeability as well as the intestines’ innate proinflammatory pathways. They have demonstrated sufficient therapeutic potential for patients who suffer from intestinal inflammatory conditions. This is especially significant given the prevalence of ulcerative colitis (one of the most common types of IBD) in India, which is atypically high for the region.191

**Drug Delivery**

Soy beans have high protein content (between 40 and 50 %) and purified soy protein (SP) contains at least 90 % protein on a dry weight basis.192 This protein can be used to make soy protein films and fibers with useful applications in tissue engineering and drug delivery, a particularly appealing option given their abundant nature and fully biodegradable, biocompatible properties. For example, SP fibers are a useful mechanism for drug sorption and release.

One study prepared SP fibers by dissolving SP in aqueous urea solution with some sodium sulfite, incubating the mixture for two days, and extruding it into a sodium sulfate solution with acetate acid before drawing, drying, and collecting the fibers. Three model drugs—Diclofenac, 5 Fluorouracil (5-Fu), and Metformin—were then loaded onto the SP fibers by both the dissolution and sorption methods. The chemical structures of these drugs are illustrated in Fig. 3.14. The dissolution method involves dissolving the drug in a molten polymer or polymer solution, while the sorption method requires drug sorption into to a fibrous scaffold after its fabrication.193 The latter method is considered preferable for SP fibers, since it generally leaves behind fewer impurities in the fibers and enables a higher efficiency of drug utilization. Afterwards, drug release was studied in phosphate buffered saline (PBS with pH 7.4) and artificial gastric juice (AGJ with pH 1.2) solutions in a shaking water bath.194

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190 Young et al. (2011).
191 Ouyang et al. (2005).
192 Gibbs et al. (2004).
193 Prabaharan et al. (2007).
194 Xu and Yang (2009).
This study showed that drug sorption onto the SP fibers was quite good and increased at higher temperatures. This is likely due to the fact that at increased temperatures, the drugs moved faster, the boundary layer on the surface of the SP fibers thinned, and there were smaller aggregates of drugs, all of which enabled quicker, easier movement of drugs into the SP fibers. Higher temperatures can also increase drug sorption by breaking strong interactions between SP molecular chains, allowing drug molecules to enter. In addition, the study found that 5-Fu and Metformin had higher drug sorption rates than Diclofenac, likely due to their smaller size. This is because smaller drugs have an easier time maneuvering through the openings in SP fibers, so they also experience faster drug sorption at a given temperature.195

When compared to polylactic acid (PLA) fibers and starch acetate (SA) fibers, which also have biomedical applications, SP fibers demonstrated faster rates of Diclofenac sorption due to the larger surface openings their fibers possess as well as stronger forces between the drug and SP fibers. SP fibers are also more hydrophilic than those of PLA or SA, meaning that SP swells and its fibers generate larger openings and wider channels, thereby facilitating faster drug sorption rates.196

Drug release in PBS was quick, with higher initial bursts from drugs loaded onto SP fibers, but PLA and SA fibers demonstrated more constant subsequent release. However, Diclofenac drug release became much more constant in the AGJ solution (compared to the PBS). Moisture levels played an important role in shaping the constancy of drug release, so that is one factor that could be manipulated in the future to achieve a desired result. Overall, soy protein fibers showed their abilities for drug sorption and release and potential relevant applications in the biomedical field.197

**Tamarind Applications**

**Drug Delivery**

Biodegradable polymers containing polysaccharides are a good option for nanoparticle carriers in drug delivery. Tamarind seed polysaccharide (TSP) can be obtained from *Tamarindus indica* plants in India and elsewhere in South and Southeast Asia. The chemical structure of TSP is shown in Fig. 3.15. Currently, TSP is used in the food industry as a thickening, stabilizing, and gelling agent.198 Modifying TSP to become carboxymethyl tamarind kernel polysaccharide

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195 Ibid.
196 Ibid.
197 Ibid.
198 Sahoo et al. (2010a).
(CMTKP) has high potential for pharmaceutical nanotechnology applications due to its greater stability and solubility in cold water. It also possesses a lower biodegradability and longer shelf life. This is particularly important for ocular drug delivery, which is considered one of the most challenging areas to scientists due the eye’s ‘‘pharmacokinetically critical environment.’’ The eye’s numerous barriers—such as the corneal epithelium, iris blood vessels, retinal pigment epithelium, and muco-aqueous layer of the tear film—decrease the amount of each pharmaceutical dose that is actually absorbed. Studies have shown that CMTKP displays excellent ocular tolerability and absorptive properties when tested with tropicamide, an agent often used during eye surgeries and examinations.

TSP has also been studied in the context of delivery of diclofenac sodium, a non-steroidal anti-inflammatory drug often used as a strong analgesic when treating conditions such as rheumatoid arthritis. Although the past few years have seen an increase in attempts to use natural polymers like alginates for drug delivery, such efforts have encountered several problems. For example, with cross-linked alginate hydrogels, the drugs might leak out during gel formation (thereby

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199 Kaur et al. (2011).
200 Duvvuri et al. (2003).
201 Diebold and Calonge (2010).
202 Kaur et al. (2011).
203 Nayak et al. (2010).
decreasing encapsulation efficiency) and the burst of released drugs is quite sharp due to the rapid in vitro degradation release process. However, blends of appropriate polymers—such as those including TSP—can increase drug encapsulation. Researchers have shown that diclofenac sodium-loaded pH-sensitive TSP-alginate composite beads are a suitable method of controlled drug delivery, particularly for pharmaceuticals with various enzymes, peptides, and other physiochemical properties.

**Ophthalmic Applications**

Cataracts, a significant health issue in developed and developing countries alike, are responsible for almost half of all cases of blindness worldwide. The situation is particularly bad in India, where surveys indicate that cataracts account for more than three-quarters of all avoidable blindness. Hence, effective treatments for cataracts are a valuable asset for global health. In addition to intraocular lens replacement, researchers have also been pursuing ways to treat the eye with pharmaceuticals.

The eye is generally impermeable to most environmental agents. The blink reflex assists with a continuous tear flow that clears the ocular surface and inhibits microorganism build-up. With their defensins, lactoferrin, lysozyme, and secretory immunoglobulins, tears also help restrict bacterial growth on the ocular surface. Although most pathogens cannot penetrate a healthy corneal layer, any sort of injury to the ocular surface—caused by anything from allergic hypersensitivity to foreign body trauma—greatly increases the risk of infections like microbial keratitis.

To combat keratitis, high drug concentrations must be maintained at the infected site. This would apply to cataract treatment as well. Ingested drugs make little sense since the cornea is not vascularized, so the most common approach today is to treat keratitis with topical drugs. At the same time, continuous tear flow limits the bioavailability of topical drugs and the corneal epithelium resists drug penetration, so treatment typically involves topical drug administration 1–4 times an hour for 2 or 3 days. Such a treatment generally requires hospitalization, is clearly inconvenient for the patient, and is also associated with toxicity to the

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204 Nayak and Pal (2011).
205 Manjanna et al. (2009).
206 Nayak and Pal (2011).
207 Taylor (1999).
208 Neena et al. (2008).
209 Haynes et al. (1999).
210 McClellan (1997).
211 Sahoo et al. (2011).
corneal epithelium in vitro. However, TSP could change this, given its demonstrated ophthalmic applications.

TSP is branched, non-ionic, and neutral, made up of a cellulose-like backbone with xylose and galactoxylose constituents. This structure lends the polysaccharide a ‘mucin-like’ molecular configuration, thereby leading to its mucoadhesive properties. TSP’s structural similarity to endogenous mucin might be what enables formulations containing the polymer to successfully adhere to the ocular surface for extended periods of time and provide relief for symptoms of dry eye. Some studies have also indicated that TSP might exceed Hyaluronic acid—a visco-enhancer sometimes incorporated in topical eye care solutions—in terms of ocular retention time, relief of dry eye symptoms, and wound healing abilities. In addition, TSP at particular concentrations is able to crystalize in a fern-like shape, increasing its similarity to natural tears.

One ophthalmic application of TSP is as a mucoadhesive polymer that enhances viscosity in order to maximize contact time between antibiotics and the tissue of the cornea. Since TSP is non-toxic to the ocular region, available on the market, a good tear fluid substitute, and an accelerant of the corneal wound healing rate, it is a good option for the ocular administration of antibiotics. Such a use would likely decrease corneal toxicity and increase patient compliance due to its simple and less frequent nature of administration.

The use of TSP for ophthalmic drug delivery is particularly appealing given its ability to release both water-soluble and –insoluble drugs in a controlled manner. The rate of drug release can be easily altered by manipulating the degree of cross-linking or using diluents such as lactose and microcrystalline cellulose. TSP as a hydrophilic drug delivery system has been proven as an effective model with the use of several drugs, including gentamicin, ofloxacin, nifedipine, and rufloxacin. This demonstrated success as well as TSP’s non-carcinogenicity, high drug-holding capacity, and excellent thermal stability all point towards favorable developments of the polysaccharide for biomaterial use in future ophthalmic applications.

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212 Sahoo et al. (2011).
213 Sahoo et al. (2010b).
214 Sahoo et al. (2011).
215 Burgalassi et al. (1999).
216 Mannucci et al. (2000).
217 Sahoo et al. (2011).
218 Ibid.
219 Ibid.
220 Ibid.
Malaria is a disease that primarily impacts low-income countries in warm climates that have limited health care facilities. Unfortunately, India fits this description well and the country is estimated to be losing approximately 200,000 lives a year to this illness.° Thus it should come as no surprise that health experts are desperate to find ways to suppress this disease and minimize its spread.

In regions as distinct as Ethiopia and India, tamarind has long been used as an antimalarial in folk medicine. Studies have revealed that such traditional treatments are not without base. Water extracts from *Tamarindus indica* fruits demonstrated high chemosuppressive properties, with over four-fifths of the malarial *Plasmodium* present suppressed at a dose of 650 mg/kg.° This could be due to the tannins, saponins, sesquiterpenes, alkaloids, and phlobatannins in the tamarind fruit that are thought to have antiplasmodial activity.° These studies have shown that tamarind extracts have substantial antimalarial properties that can be further explored and potentially developed into anti-malarial drugs or other therapeutics.

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221 Dhingra et al. (2010).
222 Mesfin et al. (2011).
223 Doughari (2006).
**Anti-Obesity**

Tamarind fruits also demonstrate impressive weight-reducing properties. After receiving a high-fat diet to make them obese, rats that were orally administered *Tamarindus indica* pulp aqueous extract (TIE) prepared from matured fruits displayed lower levels of food and caloric intake. Therefore, their mean body weight and body weight gain was far less than in the positive control group of obese rats who did not receive any TIE. In addition to decreasing the weight gain caused by a high-fat diet, TIE has also demonstrated the potential to prevent excessive weight gain.\(^{224}\) *Tamarindus indica* contains many flavonoid compounds which are considered as inhibitors of fatty acid synthase activity, which could be part of the reason why TIE has displayed such anti-obesity promise. It is also possible that the high acidic and digestible starch contents of tamarind extract alter the colonic mucosa and affect the colon’s microfloral content in such a way as to aggravate the adverse effects of a fatty diet and obese condition.\(^{225, 226}\)

**Antihelminthic**

The bark of *Tamarindus indica* has demonstrated substantial anthelmintic activity, meaning that it is effective at killing or expelling parasitic worms (helminths).\(^{227}\) This could be due in part to the tannins present in tamarind bark, which are capable of binding free proteins in the gastrointestinal tract of the host animal or glycoproteins on the parasite’s cuticle in order to kill the worm.\(^{228, 229}\) One study demonstrated the efficacy of tamarind bark extracts in expelling two types of test worms, an Indian earthworm (*Pheretima posthuma*) and an aquarium worm (*Tubifex tubifex*). The earthworm was anatomically and physiologically similar to intestinal roundworm parasites found in humans, and the aquarium worms belong to the same group of Annelida as these earthworms.

As shown in Fig. 3.16, alcohol extract from the tamarind bark at a concentration of 15 mg/mL caused paralysis at 22.33 min and death at 45.00 min for the earthworm, while inducing paralysis at 14.66 min and death at 20.66 min in the aquarium worm. This is very impressive considering each of these times was faster than the times achieved by treatment with 10 mg/mL of piperazine citrate, which was used as a reference standard. (Piperazine citrate causes muscle hyperpolarization that forces relaxation and lowers responsiveness to acetylcholine’s

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\(^{224}\) Azman et al. (2011).
\(^{225}\) Lamien-Meda et al. (2008).
\(^{226}\) Wang et al. (2006).
\(^{227}\) Das et al. (2011).
\(^{228}\) Athanssiadou et al. (2001).
\(^{229}\) Thompson and Geary (1995).
contractile action, ultimately leading to flaccid paralysis.) Therefore tamarind-based materials have demonstrated sufficient anti-helminthic properties to justify studies for applications in a clinical setting.

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