## Chapter 2

# The Immunology and Science of Mistletoe

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*"The best and most efficient pharmacy is within your own system."*
– Robert C. Peale, UK Prime Minister, mid-1800s

Plant extracts are inherently unique. Unlike synthetic drugs, which typically provide a single hoped-for targeted effect, botanical extracts naturally contain an array of compounds with multiple synergetic effects. Mistletoe therapy provides a range of constituents that simultaneously heighten immune system activity, increase the quantity of some immune cells, and directly inhibit tumor cells. In this chapter, while we explore the specifics of each effect, keep in mind that it's the synergy of all those effects together that result in substantial benefits for the patient.

This chapter is not intended as an in-depth textbook exploration of immune escape, cellular mutations, or cancer's manipulation of the immune system. All such clinical and investigative concepts are relevant to mistletoe therapy, and we do discuss them at PAAM-sponsored practitioner trainings (see "Resources"). For the purpose of this book, we will review the basics of immunology: the immune cell categories and their varied tasks. Then we'll look at mistletoe, its many active constituents, and how those constituents influence the immune response and the tumor itself.

## *Immunology basics: An overview*

You might remember the primary immune cell categories from high school or college. The human immune system, its cells and other components, are divided into two primary groups: *Innate* and *Adaptive. Innate immunity* refers to the immune system components, barriers, and cells that have always been present in you. *Adaptive immunity* involves cells that are able to learn about, identify, and address all the new pathogens you encounter from birth onward. Let's review these two classes of cells, so we can better understand how mistletoe interacts with them.

### *Innate immune system*

Natural and non-specific, I think of innate immunity as a multipurpose pocketknife. It has many tools to complete a wide array of jobs, but it probably will not work as well for a more specialized task. The innate immune system is broken down into four parts:

***Physical barriers:*** Skin and mucous membranes. Our most basic first line of defense against external pathogens.

***Immune cells:*** Specifically neutrophils, lymphocytes, dendritic cells, and macrophages. These diverse cells can engulf (through phagocytosis) or otherwise kill pathogens and cancer cells. This category includes natural killer (NK) cells—so called because they can kill a pathogen or cancer cell on their own, without activation from another cell or antibody.

***Complement:*** A vital part of the immune response consisting of circulating blood proteins. These proteins can attach to, degrade, and attract additional immune response toward pathogens. These proteins are produced by the liver; this is the reason that patients with late-stage liver disease can become prone to infection.[1]

***Alert and Communication System:*** Information shared between immune cells, particularly through messenger chemicals called cytokines. There are several types of cytokines with varied roles including mediating local inflammation, addressing viral infection,

and stimulating NK cells and macrophages. A variety of immune cells can produce cytokines, including macrophages and mast cells, as well as B-cells and T-cells from the adaptive immune system.

When considering the innate immune system's role in cancer treatment, we're especially interested in NK cells. These cells are able to recognize stressed and unhealthy cells even in the absence of antibodies. This is important because tumor cells, in an active cancer process, are often able to hide from the immune system. Since cancer cells originate from our own cells, they are often overlooked by the immune system, which is surveilling the body for foreign pathogens. But NK cells can potentially work around that and still recognize the tumor cell as a problem. The activated NK cell releases cytokines, including *tumor necrosis factor-alpha* (TNF-α). Activated NK cells also increase the activity of macrophages, dendritic cells, and neutrophils. They prompt T-cell activity and antibody-producing B-cells. They are a powerful ally, and later we'll learn how mistletoe therapy affects them.[2]

### *Adaptive immune system*

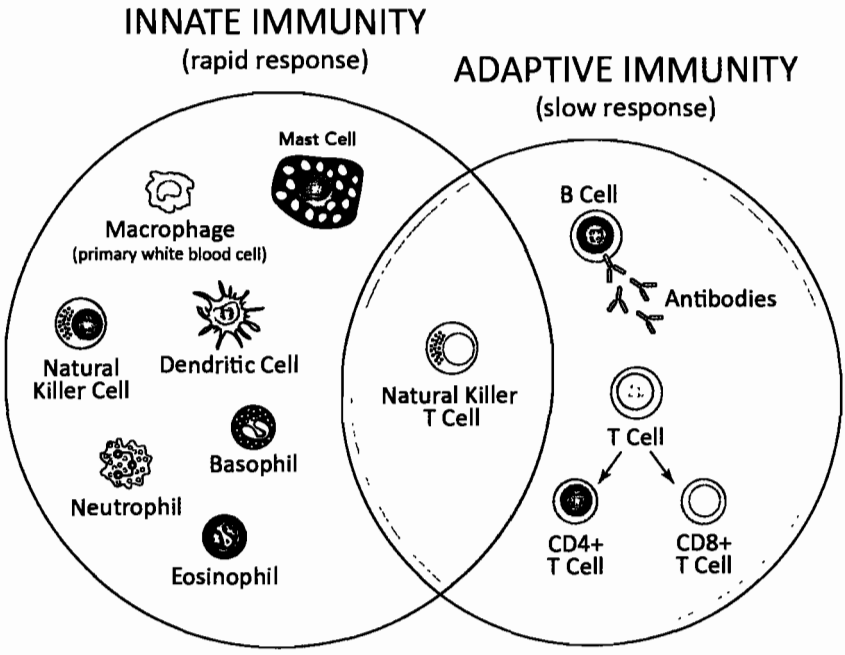
Also called the *specific* or *acquired immune response*, adaptive immunity is composed of T- and B-lymphocytes. Though highly specified in their purpose, these cells (about 2 trillion in the human body) make up 20 to 40 percent of the white blood cell mass, equivalent to the mass of the brain! There are a lot of these cells circulating in the body.

***B Cells:*** Involved in *humoral immunity*. B cells create antibodies in response to newly recognized pathogens. Antibodies are pathogen-specific; they recognize and latch onto unique proteins on the surface of a specific pathogen. This identification process can help the immune system recognize and eliminate the problem faster if ever exposed to it again in the future.

***T Cells:*** Involved in *cell-mediated immunity*. T cells are further differentiated into CD4+ cells and cytotoxic CD8+ cells. CD4+ cells are also referred to as *helper T cells*. They "help" by activating the

CD8+ cells, which are also called *killer T cells*. Those killer T cells do the actual work of eliminating pathogens (especially viruses and cancer cells), but first a helper T cell activates them. CD8+ killer T cells are of particular interest in cancer immunotherapy, because of their ability to kill tumor cells.[3]

## Difference Between Innate & Adaptive Immunity




*A healthy immune cascade*

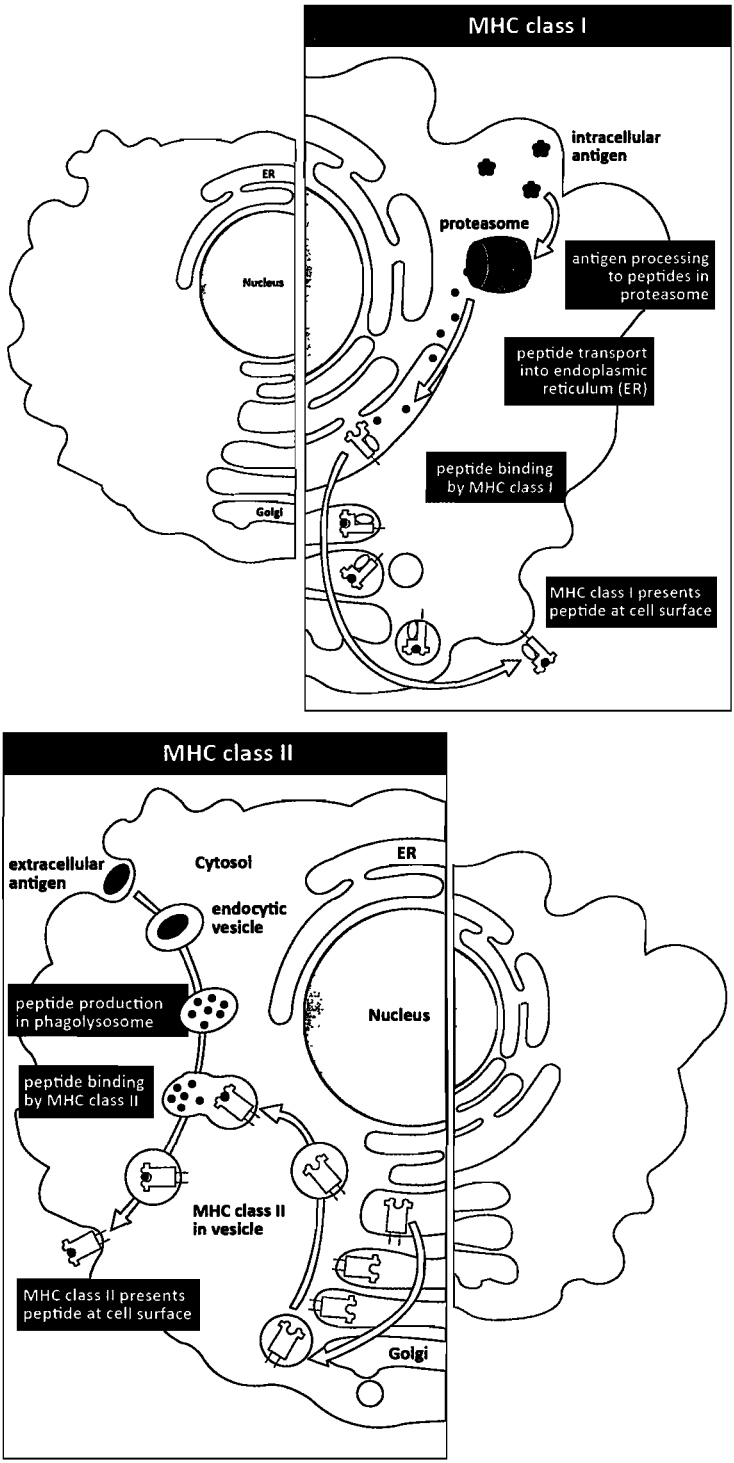
As you can see, the entire immune system is divided into two major classes, and those classes contain multiple cell types and components. We think of all these cells having individual, specified roles, but there's a lot of overlap, redundancy, and cooperation between all parts of the immune system. Some immune cells can directly kill a pathogen by inserting cytotoxic chemicals into it. Others are able to engulf parts of a pathogen, or the entire pathogen. They can destroy the problem and

"educate" the rest of the immune system about it. Yet other immune cells excel at recruiting help from the rest of the immune system. Ultimately, it's the concerted effort of all these immune system constituents that results in a successful response.

Let's consider how this works in a single pathogen encounter. For instance, when your body is exposed to a bacterial infection that it hasn't seen before, components of the innate immune system are frequently the first to find it. Circulating blood complement attaches to the bacterium. These proteins both create a "flag" of sorts and begin to degrade the surface of the pathogen. Innate immune system cells now notice the problem and proceed to destroy it. In that elimination process, macrophages and dendritic cells can present parts of the dead bacteria to the adaptive immune cells. They hold up the pathogen parts, essentially on display, so other immune cells can learn about the problem. See the image (bottom of page 33) for the detailed steps in this MHC Class II process. In this way, the *innate cells* begin sharing information with the *adaptive cells*. The adaptive cells are the ones who then record a memory of this bacterial threat. They generate and circulate antibodies for future use. In short, the *innate immune cells* begin the process of threat elimination, then the *adaptive cells* complete that process and create a record of the pathogen encounter.

Weeks, months, or years later, if this bacterium shows up again, you can actually get reinfected. "Immunity" doesn't mean you don't get infected. You do technically become infected, but your immune system memory (in the form of circulating antibodies) ensures that both innate and adaptive immune cells can attack the problem immediately. That makes for such an efficient immune response, you never even notice the infection. Your immune cells eliminated the problem before any symptoms could occur.

In the case of a viral infection, the process is similar, but with an important deviation. With viral infection, the pathogen is often *already inside* a cell—that's how viruses replicate; they need a cellular host. They're not going to be floating around outside the cells waiting to be found. This is an immune threat that's already inside the human cell.


MHC class I
intracellular antigen
ER
proteasome
Nucleus
antigen processing to peptides in proteasome
peptide transport into endoplasmic reticulum (ER)
peptide binding by MHC class I
Golgi
MHC class I presents peptide at cell surface
MHC class II
extracellular antigen
Cytosol
ER
endocytic vesicle
peptide production in phagolysosome
Nucleus
peptide binding by MHC class II
MHC class II in vesicle
MHC class II presents peptide at cell surface
Golgi

That's called an *intracellular pathogen*. It's possible for any human cell, not just immune cells, to recognize that it has a viral problem and then present parts of that virus on its own exterior surface. (See top of page 33 for the MHC Class I process.) In this scenario, there is a specific adaptive immune cell that needs to arrive on the scene to educate itself about this viral threat: *a cytotoxic T cell*, or CD8+ killer T cell.[4]

These details about virus recognition and elimination are important because *the process by which the immune system eliminates a virus is very similar to the process by which it recognizes and eliminates cancerous cells.*[5] Just as a virus can hide inside an otherwise normal human cell, so an *oncogene* can hide inside and alter a human cell. The immune system uses a similar pathway to handle both of these threats, and both scenarios lean heavily on CD8+ killer T cells. That CD8+ presence will become more significant as we look at how mistletoe interacts with the immune system.[6]

### *Where is the immune system?*

It's common to assume that all these complex responses and interactions are all happening within the circulatory system. But that's not actually the case. Only about two percent of your lymphocytes are in circulation with your blood. The rest, the vast majority, are dispersed throughout your body tissues and in your lymphatic system.[7] That makes sense, since most pathogenic threats are going to enter the body through mucosal membranes or through an insult to the skin—external pathogens don't just suddenly appear in the blood. So immune cells are present throughout body tissues. They're just below the surface of your skin, they're patrolling organs, and they're especially concentrated in the mucosal membranes of the respiratory tract and the gastrointestinal tract.

It's important to note this nuance, as it becomes quite relevant when we consider how to best administer mistletoe therapy. We'll get to that shortly. Let's first look at the active constituents in mistletoe extract and how they interact with the complexities and layers of the human immune system.

## *Mistletoe's activities: Modulating immune response and damaging the tumor itself*

Mistletoe has been used as medicine for one hundred years. For quite some time, practitioners and patients have been experiencing and observing the clinical effects. But it's really in the past decade that there's been an explosion in *Viscum album* research and investigation into how it works at a cellular and molecular level. As with any scientific inquiry, we're quickly learning what we don't know! This is an evolving knowledge base, and we hope that this chapter simply brings you up to speed on the most recent discoveries about mistletoe's best-known active constituents and their effects.

### *Mistletoe's primary constituents*

There are several significant phytochemicals in mistletoe extract, but there are two groups that appear to be doing most of the heavy lifting when we use VAE therapy. These are the *lectins* and the *viscotoxins*. The lectin proteins and polypeptide viscotoxins collectively convey both destructive effects on tumor cells and modulatory effects on the immune system. Let's define and learn a little more about these unique compounds and a few of mistletoe's other active constituents.

*Mistletoe Lectins:* The word *lectin* comes from the same Latin root as the words *select* and *elect;* it means "to choose." A lectin is, indeed, a complex protein whose molecular structure "chooses" to bind to specific carbohydrate groups on the surface of certain cells. The three primary lectins in VAE are commonly referred to as Mistletoe Lectins I, II, and III. Those three lectins have a demonstrated *apoptotic* (destructive) effect on cancer cells, with Lectin III having the strongest effect and Lectin I being milder.[8–11]

Mistletoe not only provides these three primary lectins; it is also one of the first plants ever identified to contain two classes of lectin. The three closely related lectins are joined by a fourth unique lectin, known as *chitin-binding agglutinin.* This additional lectin is less researched, but structurally similar to a lectin in stinging nettle.

In animal studies, the lectin in stinging nettle is known as a *superantigen*, which is a substance that can provoke a dramatically heightened T-cell response.[12–14] The animal studies show that even small exposure to this lectin can activate up to 20 percent of their T cells. This may explain why it takes such small doses of VAE to elicit such striking immune system effects in patients. While Mistletoe Lectins I through III potentially convey apoptotic effects directly at cancer cells, this additional lectin appears to interact more with the immune cells, heightening their activities.[15–17]

*Mistletoe viscotoxins:* Viscotoxins are regarded as plant *defensins*, compounds that plants produce to protect themselves against parasites, bacteria, and fungal infections. Human immune cells produce some similar defensin compounds, too.

Viscotoxins are especially fascinating because they preferentially bind to more depolarized or negatively charged cell membranes.[18] This is where things get quite interesting. The external surface of a healthy cell membrane is usually positively charged relative to the surface inside of the cell. The external membranes of fast-dividing problem cells (such as cancer cells) are usually more negatively charged than healthy cells.[19] That means that viscotoxins have a preference for binding to and harming the membranes of cancer cells. Once attached to the cell membrane, the viscotoxin creates a pore (hole) in the membrane. This opening allows a flood of calcium into the cell. The cell loses its structural integrity and cellular lysis (breakdown) begins. Once the pore is wide enough, the viscotoxin itself can also enter the cell space and begin binding with and destroying other cellular components.[20–24]

The most important point to take away from this introduction concerning mistletoe lectins and viscotoxins is their *selectivity*. The lectins choose (elect) to bind to specific carbohydrate structures, particularly those associated with tumor cells. Meanwhile, viscotoxins have a preference for binding with fast-dividing negatively charged cell surfaces, which are common among cancer cells.[25,26]

*Other Mistletoe Constituents:* Table 2.1 provides a list of known VAE constituents and their studied effects. The highlights include

| Structural Types | Substance Class | Effects on Tumor Cells | Effects on Immune Cells |
|---|---|---|---|
| Glycoproteins | Mistletoe Lectins I, II, and III (RIP II) | Cytotoxicity through inhibition of ribosomal protein synthesis and induction of apoptosis (intrinsic pathway). | Macrophage activation, release of TNF-α, IL-1, IL-2, IL-6, eosinophilia |
| | VisalbCBL = cbML | Weak cytotoxicity | Adjuvant increase in immune response |
| Polypeptides | Viscotoxins | Cytotoxicity through cell membrane leakage | Macrophage activation, increased phagocytosis activity of granulocytes |
| Oligo- and polysaccharides | Arabinogalactans, galacturonans | Indirect, immune-mediated tumor inhibition | Stimulation of T helper cells, increased NK cell activity |
| Flavonoids | Quercetin derivatives | Induction of apoptosis | Anti-inflammatory, antioxidant, and antinociceptive (pain relieving) effects |
| Phenylpropane glycosides | Syringin | NA | Antioxidant, stress protection, and immunoprotection (adaptogenic effects) |
| Triterpenes | Oleanolic, ursolic, betulinic acid | Induction of apoptosis and cell differentiation, anti-angiogenesis | Anti-inflammatory and antioxidant effects, immunoprotection |

*Table 2.1: Mistletoe extract (VAE) constituents and studied effects*[36]
(*Source:* Helixor Heilmittel, *used with permission*)

several oligosaccharides and polysaccharides that appear to stimulate helper T cells and heighten NK cell activity. They also help to stabilize the mistletoe lectins.[27–29] Mistletoe extract contains flavonoids like quercetin, which is known to help induce healthy *apoptosis* (normal cell death).[30,31] Mistletoe also contains a high concentration of *thiols*, including *glutathione*—which is regarded as the body's "master antioxidant" and has an important regulatory role in lymphocyte function,[32] as well as detoxification processes in the liver. Finally, mistletoe contains several triterpenes, which have been studied for their antiproliferative effects (preventing cancer from spreading) and their ability to help induce normal apoptosis.[33]

What is most striking about mistletoe extract is the complementary and synergetic nature of the entire list of actives. The power of VAE therapy doesn't rest in a single active constituent. It's the whole plant, all its actives, that work together to produce multiple apoptotic and immunomodulatory effects. There have been some cell line studies that

have seen beneficial effects conveyed by a single constituent isolated from mistletoe. However, in practice, the whole plant extract seems to be the most effective.[34,35]

### *Variation in mistletoe extract content*

Lectin content is typically more concentrated in the center of the plant, in the stems and sinker root. Lectin levels also tend to be higher in plant material that's harvested in the winter. Conversely, viscotoxins are more concentrated in the peripheral parts of the plant, not in the sinker root, and the viscotoxin levels are higher in plants harvested at midsummer.[37,38]

Harvest season matters. Plant parts matter. Whether harvest takes place during winter or summer and whether a manufacturer harvests the leaves, flowers, buds, stem, or sinker root—all these factors affect the lectin and viscotoxin content. All anthroposophic VAE manufacturers use the whole plant, combining both winter- and summer-harvested mistletoe, to acquire the broadest range of actives. When crafting their extracts, each manufacturer uses its own unique process to acquire specific active ratios. That's why pine mistletoe from two different manufacturers will differ in lectin concentration. This is actually quite useful for most mistletoe practitioners as it provides a more varied tool set when addressing diverse cancer types and patient scenarios. Chapter 4 discusses these manufacturer and host-tree differences in greater detail.

### *Mistletoe's activities as an adjuvant cancer therapy*

Now that we know some basics about the immune system, and we're aware of mistletoe's known active compounds, let's look at how VAE interacts with the immune system in the context of cancer care. In general, VAE alters multiple immune system activities, resulting in a net effect that is considered *immunomodulatory*. It neither overstimulates nor suppresses the immune system. It helps the immune system work more efficiently.

### *Direct anti-cancer effects*

As noted, when we looked at the mistletoe lectins and viscotoxins, VAE therapy provides some adjuvant (additional and supportive) effects that are directly harmful to the tumor itself. It can help:

***Induce Apoptosis:*** This is achieved through *direct* cytotoxic effects (lectins and viscotoxins can directly break down tumor cell membranes[39]) and *indirectly* by supporting the immune cells that are able to kill cancer cells (i.e., NK and CD8+ cells).[40–42]

***Limit Metastasis:*** We're still learning about the method of action, but VAE appears to reduce the cancer's ability to expand its own blood supply (anti-angiogenic effect)[43] by lowering *VEGF* (Vascular Endothelial Growth Factor, involved in blood vessel formation).[44] VAE also appears to inhibit proliferation and inhibit protein synthesis by the tumor cells.[45] All of these effects hamper the cancer's ability to spread.

***Repair and Stabilize DNA:*** When healthy cells are stressed or damaged, whether through the disease process or due to conventional treatment side effects, VAE appears to help stabilize and even repair DNA. In a *European Journal of Cancer* article, researchers postulated that "the increase of DNA repair could be due to a stimulation of repair enzymes by lymphokines or cytokines secreted by activated leukocytes or an alteration in the susceptibility to exogenic agents resulting in less damage."[46,47]

These direct anti-cancer effects are accompanied by effects on multiple immune cells. VAE therapy both damages the tumor and empowers the immune system to join in with that process of identifying and eliminating tumor cells.

### *Innate and adaptive immune system effects*

As a patient, the first tangible effect of VAE therapy is the *cytokine release.* This manifests as reddening or darkening at the injection site, which may be accompanied by some warmth and itching. This is good; it's a sign that the mistletoe therapy is working. It's

activating the immune cells, prompting them to release cytokine messengers to communicate with each other.[48] That cytokine release is just the beginning. Mistletoe's full cascade of effects on the *innate immune system* includes:

- An increase in all white blood cells, including lymphocytes, neutrophils, and monocytes[49–51]
- Improved anti-tumoral efficacy of macrophages and monocytes[52]
- Activated dendritic cells[53,54]
- Increased NK cell formation in the bone marrow and increased NK cell activity and cytotoxicity[55]

Regarding that last benefit, remember that NK cells are the ones that can work around the "masking" behavior of tumor cells. They directly identify and destroy problem cells without needing to be induced by a specific antigen. Increasing the number and activity of NK cells is highly beneficial during cancer treatment. We know from animal studies that low numbers of NK cells are associated with tumor development and progression.[56,57] Human lab studies have seen a similar connection: peripheral blood NK cell activity is significantly reduced in patients with cancer, compared to control subjects who do not have cancer.[58]

Along with these effects on innate immune system cells, VAE has simultaneous effects on the *adaptive immune response.* Mistletoe therapy appears to:

- Increase activity of CD4+ cells (helper T cells)[59]
- Increase cytotoxicity of CD8+ cells (killer T cells)[60]

VAE stimulates both helper T cells and killer T cells. While cytotoxic killer T cells are recognized for their ability to directly damage cancer cells, the helper T cells are also important. Remember, a killer T cell cannot do its work unless it is activated by a helper T cell. Because of this, the CD4+ helper T cells are sometimes referred to as the "brains" of the adaptive immune response.

As VAE therapy progresses, depending on the patient's specific treatment plan and goals, mistletoe dosage may be increased to the point of prompting temporary fever (see chapter 10). As we discussed in chapter 1, and we'll continue to touch on throughout this book, fever is an indication of a healthy, active immune response. Fever is not a disease or something we should constantly suppress. In fact, spontaneous remission and regression of cancer due to fever has been documented in hundreds of publications.[61]

### *Anti-inflammatory effects*

Within integrative oncology and anthroposophic medicine, mistletoe is perhaps best-known for prompting that initial acute cytokine release and for its use as a fever therapy. Cytokine release and fever are regarded as *pro-inflammatory* effects. So, what's this about *anti-inflammatory* effects? Realize that inflammation is not a one-step, binary process. Ideally it is a multi-step cycle within a healthy immune response, involving a constantly changing list of cells and mediators. Cytokine release is only one of several steps within an initial acute inflammatory response. So is achieving a fever. These *acute inflammatory states* can be healthy when they're part of a flowing process, when they're transient. These are actually highly desired effects in a situation where immune response (including a healthy inflammation cycle) has become compromised.

That said, yes, VAE has also been found to convey selective *COX-2 inhibition*—a well-researched and defined *anti-inflammatory* benefit. When considering multiple effects that seem both pro-inflammatory and anti-inflammatory, it's useful to understand the difference between *acute* and *chronic* inflammation:

> ***Acute inflammation*** is a transient state that can involve cytokine release and fever. These states actually promote heightened immune function. We see a cycle of heightened immune activity, followed by full resolution and reduced activity.
>
> ***Chronic inflammation*** occurs when the body gets stuck at a certain point in the inflammatory process. This type of inflammation

is degenerating and does not promote overall health. Upregulated COX-2 is often a sign of chronic degenerating inflammation.

COX-2 is often highly induced and upregulated in cases of poor cancer prognosis. We need more research to elucidate how VAE helps tamp down COX-2, and we're still learning about the connections between chronic inflammation and cancer. For now, it's one of mistletoe's many fascinating side-benefits: COX-2 inhibition without the side effects of common pharmaceutical inhibitors.[62] This is especially relevant for colon cancer where we do know that upregulated COX-2 is a hallmark of that cancer's progression.[63]

### *Overall immunomodulation*

The net effect of all these activities is immunomodulatory in nature. Looking at table 1 (page 37) we notice the stimulation of B cells and T cells, cytokines and granulocytes, and NK cells and macrophages. We see VAE helping to unmask tumor cells that are hiding from the immune system. We see immune stabilization—neither overstimulating nor suppressing the response. Simultaneously, some of the mistletoe compounds are directly cytotoxic to tumor cells. Others provide DNA stabilization and neuroendocrine effects. The entire array translates into VAE's best known net benefit: *increased quality of life (QOL).* Whatever the primary treatment course, providing VAE therapy as an adjuvant can provide better treatment outcomes[64,65] and mitigate common conventional treatment side effects.[66–68]

## *Administration considerations: Applying a better understanding of the immune system and VAE composition*

We've taken a brisk journey through the immune system, the mistletoe extract constituents, and how those constituents interact with tumor cells and immune cells. This understanding equips us to address some more nuanced questions that often come up regarding VAE therapy.

### *Subcutaneous vs. IV administration*

As practitioners, we often hear from patients and other practitioners who want to know if they should even bother with subcutaneous (SC) VAE injections. Isn't it always more effective to administer natural therapies via IV? That's not necessarily the case with mistletoe. Remember, 98 percent of your T cells are in your body tissues—not in the blood—and SC injections target the immune cells that are embedded in that space just below the surface of the skin.

The answer to the question is that both administration routes (SC and IV) are highly valuable, but in different ways. SC injections should not be viewed as a "lesser therapy." In addition to targeting immune cells in the tissue space, SC injections are useful for priming the body for a more systemic IV administration. This is especially beneficial for patients who are in a seriously weakened state. SC injections are also portable; they can be done at home, which makes it easier to complete treatment if the patient lives far from the mistletoe practitioner's clinic. IV administration can deliver higher concentrations of VAE, which is desirable in certain clinical situations. Some patients experience more hoped-for results through SC injections, some through IV therapy. More often I see the best success with patients who utilize both administration methods. Reaction to SC VAE injections can also be enhanced directly by administering IV mistletoe on the same day, which can be experienced as deeply strengthening for the patient.

### *Allergy concerns*

Latex, banana, avocado, kiwi, and chestnuts have lectin structures similar to those found in mistletoe extract. Cross-reactive allergy is a concern, even though it is quite rare. The Anamnestic Form from Helixor® (see appendix C) screens for allergy concerns. Additionally, a skin prick and intradermal test are recommended prior to starting any patient on VAE therapy. If allergy potential is mild, I know of practitioners who will give patients the option to move forward with IV

mistletoe, but preload the IV with *Quercus Cinis*, an anthroposophic remedy that inhibits the allergic response.

### *Choosing mistletoe extracts based on lectin content*

After ruling out allergy and deciding on administration routes, the next priority is choosing the right extract based on lectin concentration and host tree species. This book devotes a whole chapter to that matter (see chapter 4). We'll look at VAE brands available in the U.S., the specific host tree extracts, and how they all differ in composition. Those differences do matter. Mistletoe practitioners are trained to select the right extract for the right patient based on tumor type and based on the patient's entire constitution, their treatment goals, and their greatest obstacles at this point in their cancer journey.

Before we head into that exploration, chapter 3 will share recent clinical studies investigating VAE therapy. Using what we've learned in this chapter, we can better understand the research methods and studied outcomes, along with the implications for us as we use mistletoe in cancer care today. Let's take a look at how all the active constituents in mistletoe manifest as measurable outcomes in cancer research, tangible benefits in the lives of patients, and successful strategies at integrative oncology centers around the world.