PREFACE
Cancer is a growing health problem around the world, particularly with the steady rise in life expectancy. According to a recent report by the World Health Organization (WHO), there are now more than 10 million cases of cancer per year worldwide. Cancer derives from a collection of multiple genetic aberrations, and the same can be said as to the development of metastasis. When cancer is detected at an early stage, before it has spread, it can often be treated successfully by surgery or local irradiation, and the patient will be cured. To win the fight against cancer, it is necessary not only to develop strategies to kill all cancer cells efficiently but also to attempt to stimulate an immune response so that the immune system can keep residual tumour cells in check (Immunological aspects of cancer chemotherapy).

A causal connection between inflammation and cancer has been suspected for many years. Approximately 20% of all human cancers in adults result from chronic inflammatory states and/or chronic inflammation, which are triggered by infectious agents or exposure to other environmental factors, or by a combination thereof. There is also emerging evidence that inflammation is crucial for the aetiology of cancer (inflammation in prostate carcinogenesis, Nat Rev. Can. Angelo M. De Marzo 2007). Because NF-κB becomes activated in response to inflammatory stimuli and its constitutive activation has been associated with cancer, NF-κB might also serve as the missing link between these two processes. Although NF-κB target genes have been most intensely studied for their involvement in immunity and inflammation, this transcription factor also regulates cell proliferation, apoptosis and cell migration.

Increased incidence of solid tumours in immunosuppressed patients, reports of spontaneous tumour regression, and the positive prognostic impact of tumour-specific cytotoxic T lymphocytes or antibodies support the idea that the immune system has an effect on tumour progression in humans. Cancer cells can grow by escaping from the attack of immune cells, thus disrupting the host immune system, which is progressively suppressed as a result of tumour progression and metastasis. Tumour cells employ several mechanisms to evade immune response including loss of tumour antigen, alteration of HLA class I antigen, defective death receptor signalling, lack of co-stimulation, production of immunosuppressive cytokines and immunosuppressive T cells.
Metastasis, the spread of cancer cells from the primary tumour to distant organs and their treatment-resistant proliferation in multiple locations, remains the major clinical and biological challenge and is the main reason that leads to the mortality in the patients. The past decades have seen a significant progress in understanding the molecular and cellular mechanisms of cancer metastasis and development of new diagnostic, prognostic and predictive tools.

As a primary tumour grows, it needs to develop a blood supply that can support its metabolic needs; a process called angiogenesis. These new blood vessels can also provide an escape route by which cells can leave the tumour and enter into the body’s circulatory blood system; known as intravasation. Tumour cells might also enter the blood circulatory system indirectly via the lymphatic system. The cells need to survive in the circulation until they can arrest in a new organ; here, they might extravasate from the circulation into the surrounding tissue. Once in the new site, cells must initiate and maintain growth to form pre-angiogenic micrometastases; this growth must be sustained by the development of new blood vessels in order for a macroscopic tumour to form.

The process of metastasis, collectively known as the metastatic cascade, in which a number of steps have to be completed by cancer cells in order to successfully establish a metastatic focus at a distant location. The process, although intimately linked to genetic mechanisms, is also orchestrated by the interaction between cancer cells and its surrounding environment. The metastatic spread of breast cancer cells follows two main routes: the vascular and the lymphatic. A number of cellular structures are known to participate in the control mechanisms by which cancer cells metastasise. Those well-established ones include the cytoskeletal system, cell adhesion (both cell–cell and cell–matrix), and matrix-related mechanisms.

Metastatic cells need to detach from the primary site and attach at the secondary site. Thus it needs an intricate expression control of various adhesion molecules on the cell surface in space and time. Specific families of adhesion molecules whose expression correlates with metastasis include selectins, integrins, lectins, and cadherins.

The degradation of the extracellular matrix is mediated by a number of families of extracellular proteinases. These families include the serine
proteinases, such as the plasminogen-urokinase plasminogen activator and leukocyte elastases, the cysteine proteinases, like cathepsin D and L, and the zinc-dependent matrix metallo-proteinases (MMPs). There are many observations from various research groups highlighting the central role of MMP-driven extracellular matrix remodeling in different types of cancers. High levels of MMP-2 and MMP-9 have been found to correlate with poor outcome in patients with breast cancer, and the ratio of active to latent form of MMP-2 increased with tumour progression in invasive breast cancers.

Apoptosis, the cell-death programme that is mediated by proteases called caspases, is essential for tissue homeostasis, and its perturbed regulation underlies many diseases, including cancer. Commitment to apoptosis in response to diverse physiological cues and cytotoxic agents is governed by proteins of the Bcl2 family (The Bcl2 family regulators of the cellular life or death switch. Corry, S. 2002). Impaired apoptosis is a central step towards neoplasia. Pro-survival Bcl2-like proteins can promote tumorigenesis, Impaired apoptosis is a significant impediment to cytotoxic therapy. The mutations that favoured tumour development dampen the response to chemotherapy and radiation, and treatment might select more refractory clones.

Several of the cancer chemotherapeutics that are used today are also used as immunosuppressants for the treatment of severe systemic autoimmune diseases. This applies to cyclophosphamide which impair the proliferative and/or effector functions of peripheral T cells. Also the sudden and systemic release of numerous dying tumour cells resulting from chemotherapy might have deleterious consequences on subsequent tumour-specific immune responses.

Natural plant products have played a pivotal role in the health care of many cultures, both ancient and modern. For centuries, drugs were entirely based on natural origin and composed of herbs, animal products and inorganic materials. Medicinal plants played a prominent role in traditional systems of medicine such as Chinese, Ayurveda, and Egyptian, which are still in common use today. *Aerva lanata* is a common medicinal herb in India, Ceylon, tropical Africa, Java and Philippines, belonging to the family *Amaranthaceae*. It is used in Indian folk medicine as a demulcent, diuretic, to clear uterus after delivery, to prevent lactation and in treatment of lithiasis, diabetes mellitus, urinary calculi,
hematemesis, bronchitis, nasal bleeding, cough, scorpion stings, fractures and spermatorrhoea. 10-Methoxycanthine-6-one is a β carboline alkaloid from the plant *Aerva lanata*. Structurally related compounds like 1-Methoxycanthin-6-one have been reported to induce apoptosis in human leukemia (Jurkat), thyroid carcinoma, and hepatocellular carcinoma cell lines. Thujone, a monoterpenoid ketone, occurs in nature as a mixture of α-(−)- and β-(+) -diastereoisomers, in the essential oils and parts of the plants of Artemisia, Salvia, Thuja and Juniperus species. In this study the whole plant ethanolic extract of *Aerva lanata*, as well as the compounds 10-Mehoxycanthine-6-one and Thujone were analysed for immunomodulatory activity as well as the ability to inhibit the process of metastasis, using *in vivo and in vitro* systems.