Born in Grodzisk, Poland, Rav Shapira was the youngest son of the Chasidic Rebbe, Elimelech of Grodzisk. His father died when he was just a year old and he was taken and educated by his grandfather. In his house, Yeshayahu received an education deeply rooted in Chasidism, being groomed to take over his father's rather substantial following. Part of his education included the nurturing of a deep love for Eretz Yisrael (if not for Zionism) and when the time came to become Rebbe, Rav Shapira decided to go to Eretz Yisrael instead. Upon arriving in Jaffa, he met with Rav Kook, who had a tremendous influence on the young Chasid. Unfortunately, World War I broke out and Rav Shapira decided he should be with the family he had left behind in Poland.

There, Rav Shapira began to teach the ideas of Religious Zionism among the various Chasidic communities and he began his involvement in Mizrachi. He joined the First Mizrachi Convention of 1917 and called upon all Orthodox Jews to sell their businesses and possessions and go and live in Eretz Yisrael. He became convinced that agriculture and farming were the surest ways to reclaim the Land of Israel and to bring about the Redemption. In 1919, he spoke to the Congress in Hebrew and reiterated the Religious Zionist stance, concentrating on the need to establish agricultural settlements.

In 1920, Rav Shapira came on aliyah and immediately took over as head of the Immigration and Labor Department at the World Mizrachi Headquarters in Jerusalem. In this capacity, he initiated the building of the Rosh Pina-Tangah Road and the cleaning of Solomon's Pools outside of Bethlehem. Personally participating in these efforts, he soon became known as the Pioneer Rebbe. In addition, he began a movement to help people who couldn’t find work, thereby combating problems of unemployment.

In 1921, he took part in what was to become the foundation meeting of HaPoel HaMizrachi. He was one of the chief instigators behind the creation of a Religious Zionist Labor movement to answer the needs of religious youth who wished to fuse their lives (which were dedicated to Torah) with the Labor ideology. At the first HaPoel HaMizrachi Congress in 1922, Rav Shapira was the keynote speaker and soon became one of the Movement’s three directors, as well as head of its Settlement Division. Although most of his energies were devoted to establishing Religious Zionist Labor communities, he continued to serve on the board of the Mizrachi Party. When HaPoel HaMizrachi became embroiled in its first identity crisis, Rav Shapira supported the faction which desired to enter the general Labor Movement, i.e., the Histadrut. After the crisis had passed, he devoted his time to buying land for settlement. However, he continued to represent HaPoel HaMizrachi at inter-governmental meetings and in public forums.

In 1924, Rav Shapira traveled back to Poland to try and influence some of the Chasidic community to come to Eretz Yisrael. To this end, he was largely successful in convincing two fairly young rebbes, Rabbi Yehezkel Taub and Rabbi Israel Hoffstein, to move to Israel with their chassidim. They bought land with the help of Rav Shapira and founded the settlements of Nachalat Yaakov and Avodat Yisrael, which later merged into Kfar Chasidim. He went on to found Kfar Ata.

For 10 years, from 1933-43, Rav Shapira managed Zerubavel, a cooperative bank in Yerushalayim. But desiring to reenter agriculture, he settled in Kfar Pines, where his home served as a spiritual center for HaPoel HaMizrachi until his death in 1945. He wrote many articles on economic and agricultural problems, often foreseeing the problematic halachic issues to emerge with the new State. Synagogues in Kfar Pines, Kfar Ata and Tel Aviv were named after him, as well as a forest in the Galilee.